Joint Pulmonary-Allergy Drugs and Drug Safety and Risk Management Advisory Committee Meeting

FDA Introductory Remarks

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Division of Pulmonary, Allergy, and Rheumatology Products
Center for Drug Evaluation and Research
Food and Drug Administration
December 10, 2015

Objective

- Discuss the safety of codeine for cough or pain in children 18 years of age and younger
- Focus on safety
- Input on further restriction of use in children
  - cough
  - pain
  - over the counter availability

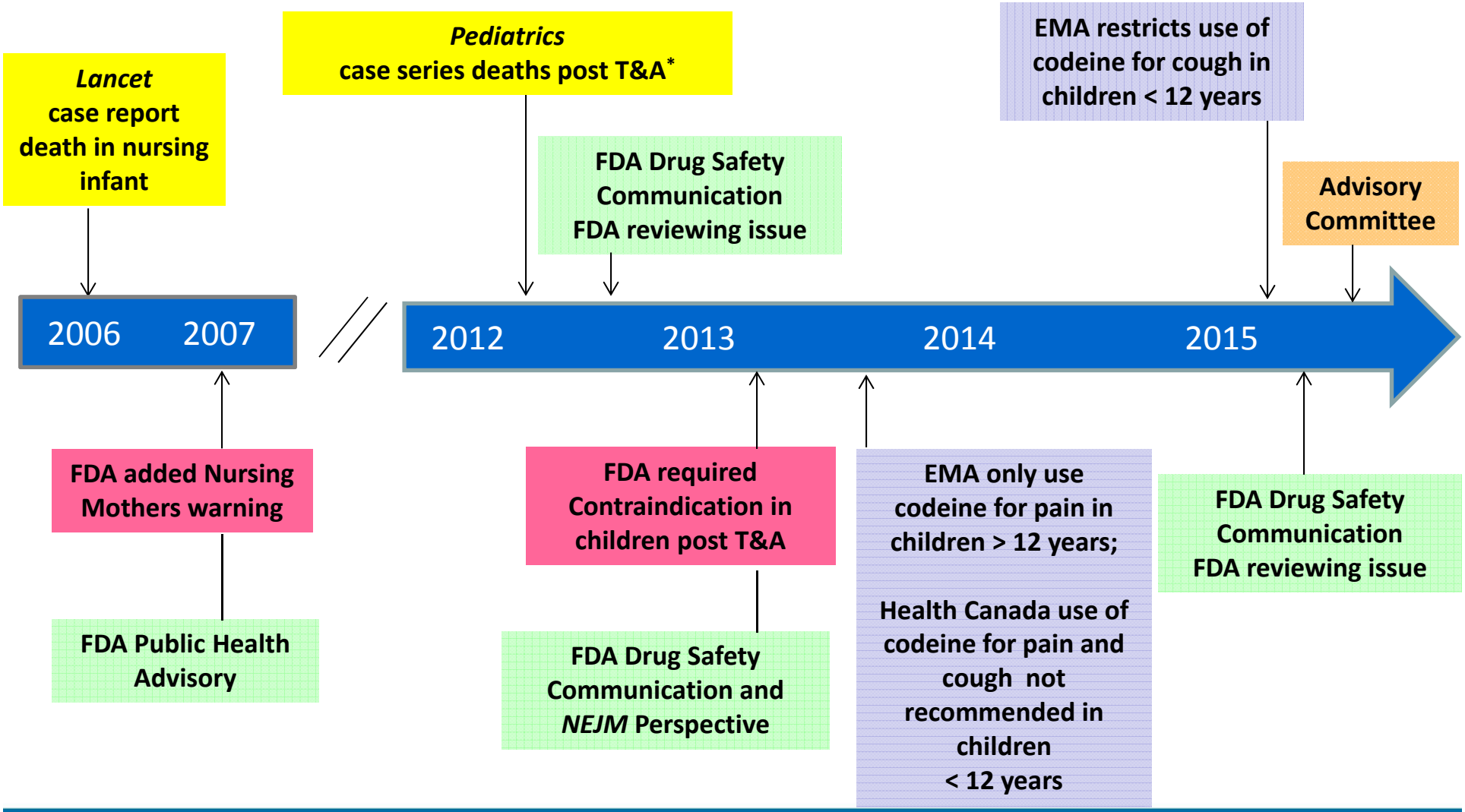
Codeine

- Opioid
  - metabolized to morphine by CYP2D6
- Relief of mild to moderately severe pain where the use of an opioid analgesic is appropriate
  - primarily in combination with acetaminophen
- Relief of cough associated with upper respiratory allergies or common cold
  - only in combination with other medications (e.g. antihistamines)
    - prescription
    - over the counter (OTC) through FDA Monograph

Issues

- Reports of respiratory depression and death in pediatric patients
- Variability in codeine metabolism based upon CYP2D6 activity
- Some regulatory agencies have restricted use of codeine for both cough and analgesia in pediatric patients

Relevant Regulatory History



Koren et al. Lancet 2006; 368:704 Kelly et al. Pediatrics 2012; 129:1343-7 * T&A = tonsillectomy and adenoidectomy

Regulatory Agency Actions

Agency	Analgesia	Cough
Australian Therapeutic Goods Administration	Contraindicated <12 years of age	Contraindicated <12 years of age
	Contraindicated for children (all ages) post adeno-tonsillectomy	
European Medicines Agency	Contraindicated <18 years of age undergoing tonsillectomy and/or adenoidectomy for obstructive sleep apnea	Contraindicated <12 years of age
	Only use in children >12 years of age	Not recommended in children/adolescents 12-18 years who have breathing problems
Health Canada	Not recommended <12 years of age	Not recommended <12 years of age
	Caution for children (all ages) with compromised respiratory function	Caution for children (all ages) with compromised respiratory function
Food and Drug Administration	Contraindicated for children (all ages) post-operative pain management post tonsillectomy and/or adenoidectomy	

Agenda

- FDA Presentations
  - Clinical pharmacology and pharmacogenomics of codeine
  - Codeine for analgesia; regulatory history through 2012
  - Codeine for cough (OTC); monograph
  - Clinical considerations for codeine as an antitussive
  - Drug utilization patterns
  - Postmarketing safety data
  - Epidemiologic data
  - Summary of safety data
- Open Public Hearing
- Charge to the Committee
- Committee Discussion

Note

No FDA presentation on efficacy

Sponsors declined to participate

Topics for Discussion

- Available safety data for codeine
- Restriction for use in children
  - cough
  - analgesia
- Codeine availability OTC through the monograph

Thank you

Clinical Pharmacology and Pharmacogenomics of Codeine

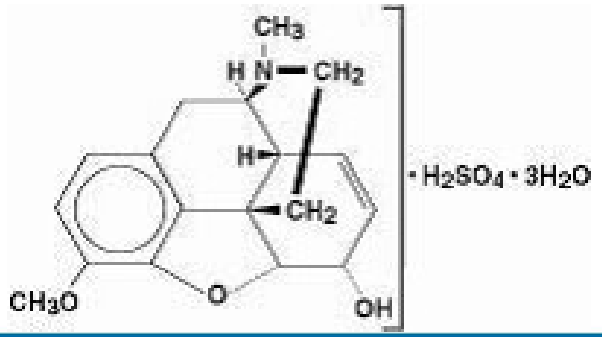
Sheetal Agarwal, Ph.D., RAC
Office of Clinical Pharmacology
Office of Translational Sciences
CDER/FDA

Outline

- Codeine Pharmacology
- Codeine Pharmacokinetics
- Codeine Metabolic Pathways
- CYP2D6 Polymorphisms
- Key Points

Codeine Pharmacology

- Naturally occurring opium alkaloid
- Analgesic use
  - Demethylated to morphine for primary analgesic effect
  - 200 fold weaker affinity than morphine for mu opioid receptor
- Antitussive use
  - Depresses the cough reflex by direct effect on the cough center in the medulla

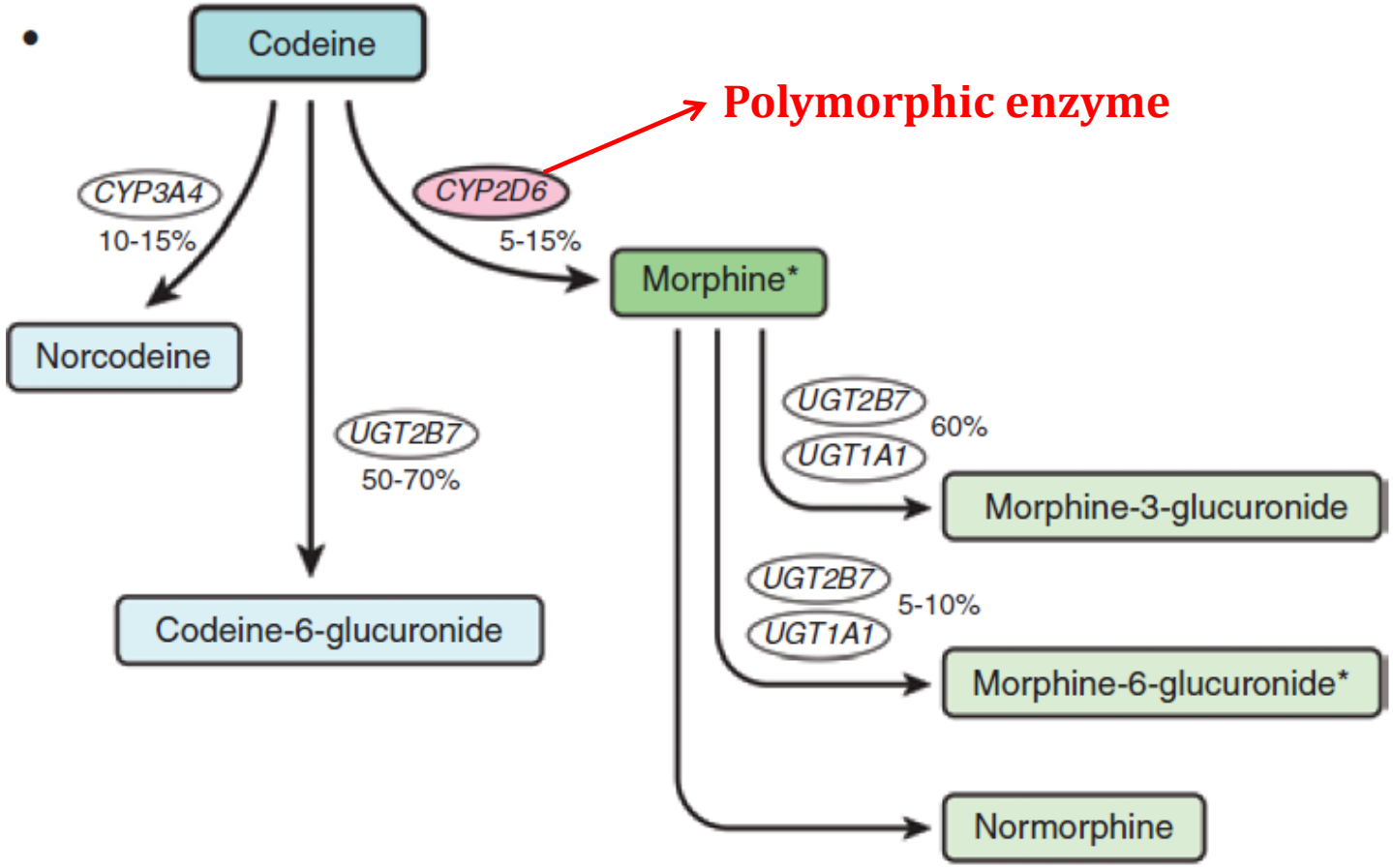


Codeine
C18H21NO3
MW 299.36

Codeine Pharmacokinetics

- Absorbed quickly, Cmax occurs at ~ 1 h
- Plasma half life is ~3 h
- Majority metabolized into glucuronide metabolites and ~20% into CYP metabolites
  - CYP3A4 mediated metabolism forming norcodeine (~10%)
  - CYP2D6 mediated metabolism forming morphine (~10%)
- Drug interaction potential with CYP3A4 inhibitors (e.g., clarithromycin, ketoconazole, ritonavir) and CYP2D6 inhibitors (e.g., paroxetine, quinidine, fluoxetine)
- Renally eliminated
  - ~10% unchanged codeine

Codeine Metabolic Pathways



*Pharmacologically active

Crews KR et Al. *Clinical Pharmacology and Therapeutics*. 2014

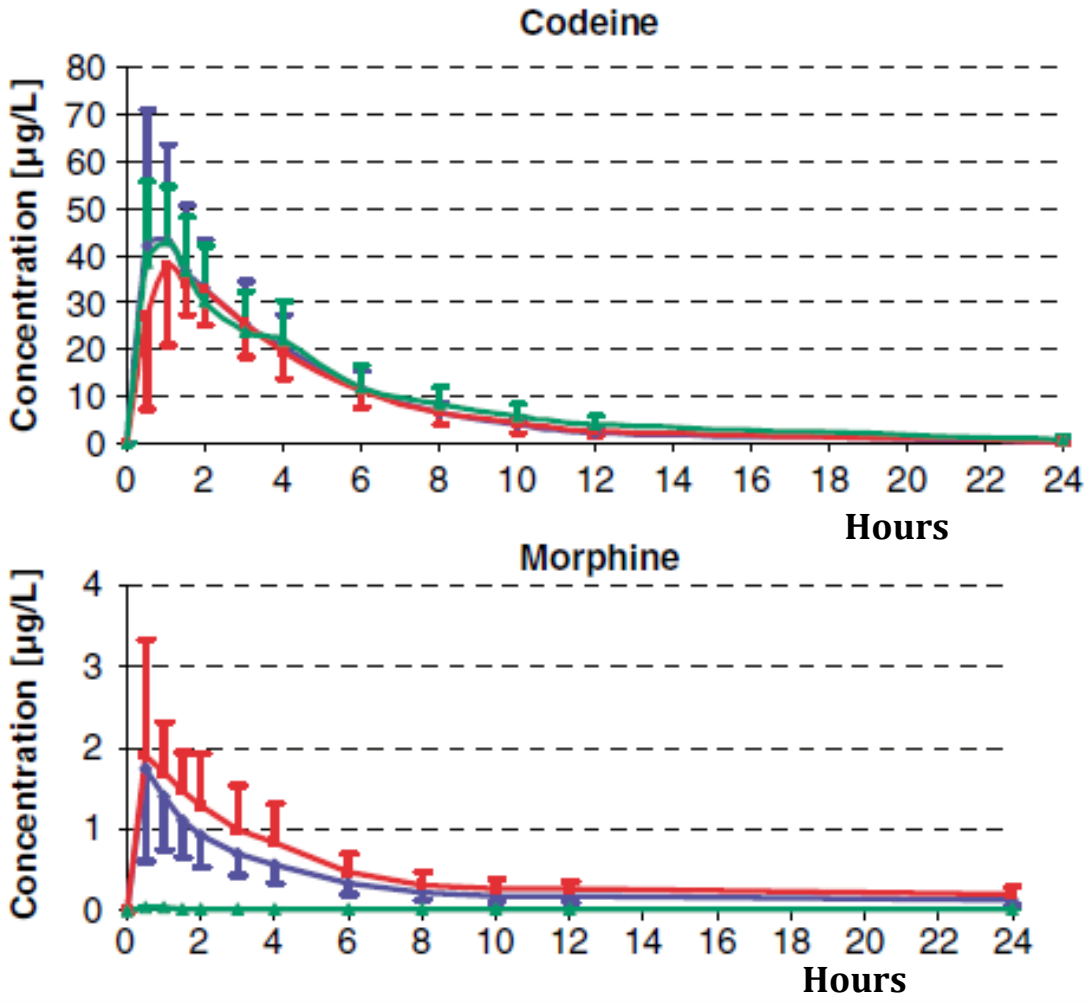
CYP2D6 Polymorphisms: 4 Phenotypes

Phenotype	Prevalence in Caucasians	Genotype
Poor metabolizer (PM)	5-10%	No functional alleles
Intermediate metabolizer (IM)	2-11%	1 reduced and 1 non-functional allele
Extensive metabolizer (EM) **WILD TYPE**	77-92%	2 alleles encoding full or reduced-function; or one full function allele with either one nonfunctional or one reduced-function allele
Ultra-rapid metabolizer (UM)	1-2%	More than 2 copies of functional alleles

UM Prevalence (%) in Other Ethnic Groups	
African American	3
Arab Ethiopian N. African	16-28
Chinese Hispanic Japanese	0.5-1

Crews KR et Al. *Clinical Pharmacology and Therapeutics*. 2012

Mean Plasma Profiles of Codeine and Morphine in CYP2D6 Polymorphic Groups

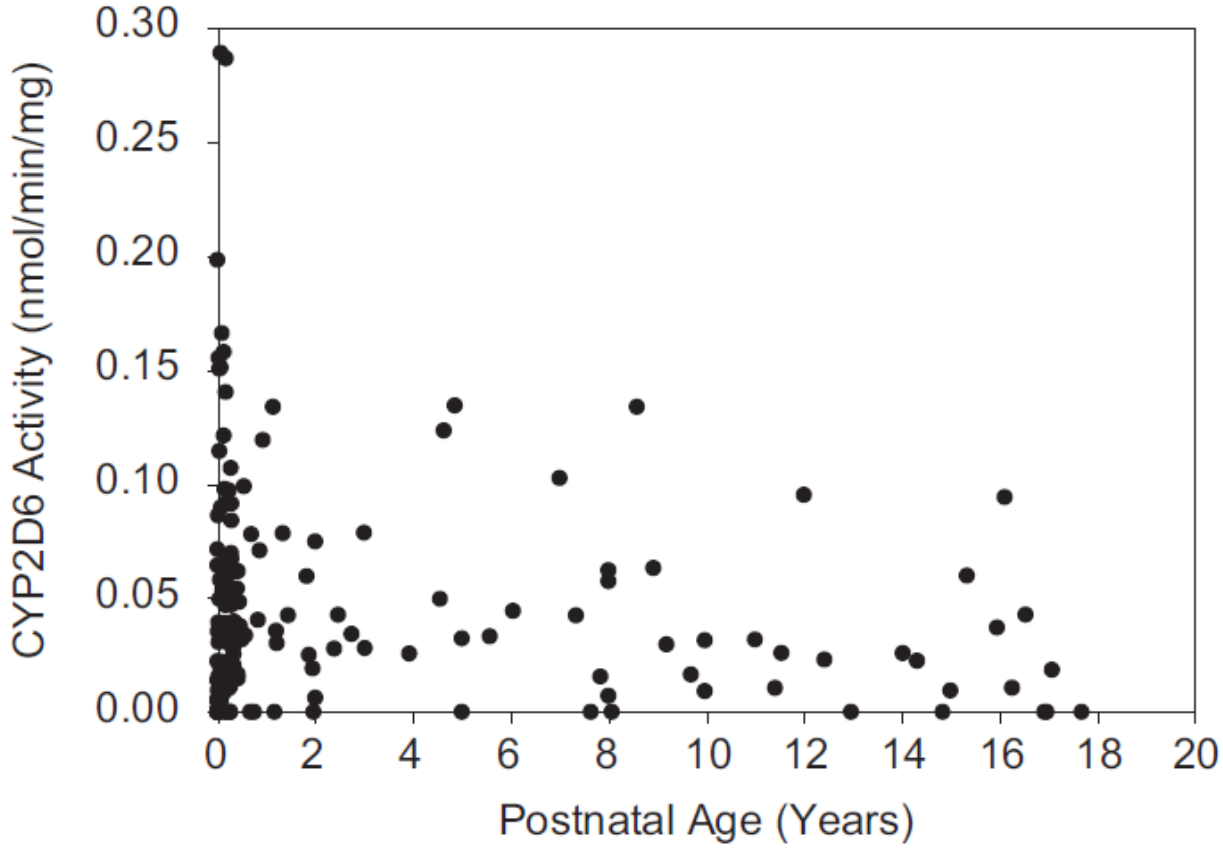


Median codeine AUC values are 180, 191 and 192 mcg.h/L in PM, EM and UM respectively

Median morphine AUC values are 0.5, 11 and 16 mcg.h/L in PM, EM and UM respectively

Kirchheiner J et al. *The Pharmacogenomics Journal* 2007.
30 mg single dose administered to 12 UM, 11 EM and 3 PMs

CYP2D6 Activity: No Significant Differences 'After 1 Week Postnatal Age'



Dextromethorphan O-demethylase activity observed in individual postnatal liver samples as a function of postnatal age
Stevens et al., DMD 36:1587–1593, 2008

Key Points

- Codeine is metabolized to a much more potent metabolite morphine, by a polymorphic enzyme, CYP2D6
- As compared to EMs, exposures of morphine tend to be higher in UMs and lower in PMs
    - Overlapping exposure values of morphine in EMs and UMs
- CYP2D6 activity does not seem to change with age

Thank You!

Codeine for Analgesia; Regulatory History of Codeine Safety in Children through 2012

Timothy Jiang, MD, PhD
Medical Officer
Division of Anesthesia, Analgesia, and Addiction Products
Center for Drug Evaluation and Research
FDA

Agenda

- **Codeine formulations**
- Safety issues affecting pediatric patients
  - Medical literature
  - AERS data
  - AAO-HNS survey
- Drug utilization -summary of 2012 review
- FDA regulatory actions
- Other regulatory agency actions

Codeine Analgesic Formulations

- Available as single ingredient
  - not approved for use in children less than 18 years
- In combination with acetaminophen
  - codeine/acetaminophen combination products are labeled for pediatric use with dosing instructions down to three years of age

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Neonatal Toxicity Related To Ultra-rapid Metabolism Of Codeine In The Mother

- August 2007:
  - Press release and public health advisory – "Use of Codeine By Some Breastfeeding Mothers May Lead To Life-Threatening Side Effects In Nursing Babies" based on published case*
  - Labeling of codeine-containing products updated to describe this risk

*Koren et al. Lancet 2006; 368:704.

Pediatric Toxicity- Medical Literature

- 2012 Kelly et al
  - 4 yr old First Nations' (indigenous peoples of Canada) boy received codeine post adenotonsillectomy (AT) for obstructive sleep apnea (OSA) and recurrent tonsillitis; died on postop day 2
    - Cytochrome P450 (CYP) 2D6 ultra-rapid metabolizer (UM) by genotype
  - 3 yr old girl of Middle Eastern descent received codeine/acetaminophen post AT for OSA; found unresponsive on postop day 2; resuscitated at hospital.
    - CYP2D6 extensive metabolizer (EM) by genotype; morphine level consistent with UM phenotype
  - 5 yr old boy received codeine/acetaminophen post AT for recurrent tonsillitis and snoring; died on postop day 1
    - Likely CYP2D6 UM by high blood morphine concentration relative to codeine

Kelly et al. Pediatrics 2012; 129:1343-7.

Other Cases In The Medical Literature Describing Codeine Toxicity In Children

- 2007 Voronov et al
  - 29-month old boy of North African descent received codeine/acetaminophen post AT for recurrent tonsillitis and mild-moderate sleep apnea; found unresponsive on evening of postop day 1; resuscitated
    - EM-UM by genotype

- 2009 Ciszkowski et al
  - 2 yr old boy received codeine/acetaminophen after AT for OSA; died on postop day 2
    - UM by genotype

Voronov et al. Paediatric Anaesthesia 2007;17:684-687. Ciszkowski et al. NEJM 2009;361(8):827-828.

Other Cases In The Medical Literature Describing Codeine Toxicity In Children (2)

- 2008 Hermanns-Clausen et al
  - Codeine used as an antitussive agent
  - 3 yr old twin boys received codeine drops for cough, once daily x 6 days. One twin died; the second twin was found apneic and was resuscitated.
  - EM by genotype
  - Analysis of size of drops suggested possibility of inadvertent overdose

Hermanns-Clausen et al. European Journal of Pediatrics 2009;168:819-824.

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2012 Adverse Event Reporting System (AERS) search

- Search strategy:
  - Time span: 1969-May 1, 2012
  - Active ingredient: codeine
  - MedDRA search terms
    - Outcome "death"
    - High Level Terms "overdoses", "death", and "sudden death."
  - Age range: children 0-17 years old
  - Intentional overdoses were excluded from consideration.

2012 AERS Search - Results

- 7 literature cases already described were the cases submitted to AERS that mentioned CYP2D6 status
- 6 other AERS cases of death did not mention CYP2D6 status
  - Two deaths occurred in children following AT;
    - 9 year old boy with significantly enlarged inferior turbinates and adenoids
    - 5 year old girl with a chromosomal disorder
      - The report stated she had high levels of morphine, codeine, and acetaminophen in her blood.
  - One death in a 2 year old boy with a history of convulsions treated with codeine for oral aphthae
    - Toxicological results showed high levels of codeine and morphine in postmortem plasma samples.
  - One death in a hospitalized child who was receiving valproic acid and codeine for an unknown indication.
  - The other two deaths occurred in children receiving codeine for cough or sore throat.

AERS Review 2012 - Other Opioids

- Same AERS search strategy was used to look for cases with hydrocodone, oxycodone, or morphine.
- No similar cases to those described for codeine were identified.

Initial Drug Safety Communication- August 2012

- In August 2012, FDA posted a DSC to inform the public that in response to the publication of the Kelly paper in Pediatrics (April 2012), we were conducting a safety review of codeine
  - Are there settings other than post-tonsillectomy where these cases occur?

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Summary Of Information From American Academy Of Otolaryngology- Head And Neck Surgery (AAO-HNS) Survey

- The Patient Safety and Quality Improvement Committee of the AAO-HNS surveyed physician membership regarding bad outcomes following tonsillectomy, such as death or permanent disability.
- 8 pediatric cases classified as being related to opioid medications
  - Indication: OSA (6), chronic tonsillitis (1), unknown (1)
  - Underlying condition: Down's syndrome (3), neurologic disorder (1)
  - Outcome: deaths (7), anoxic brain injury (1)
  - UM status: confirmed in post-mortem exam (1); suspected due to high morphine levels (1)

Goldman et al. Laryngoscope 2013;123:2544–2553.

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Summary of Drug Utilization – 2012 review

- Nearly all use of codeine for analgesia in children was as a combination product with acetaminophen
- Analysis of prescribing specialty
  - General Practitioner/Family Medicine/Doctor of Osteopathy was the top prescribing specialty for oral solid formulations of acetaminophen/codeine combination products
  - Otolaryngologist was the top specialty for oral liquid formulations for acetaminophen/codeine combination products
- Analysis of diagnosis codes associated with the use of acetaminophen/codeine combination products in pediatrics
  - Most common diagnosis code: "Surgery Follow-Up"
  - Although not commonly mentioned, drug uses associated with "Acute Tonsillitis" and "Chronic Disease of Tonsils and Adenoids" were captured

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Why Did FDA's Regulatory Action Focus On The Post-Adenotonsillectomy Setting?

- Well documented cases in the post-AT setting
- No well documented cases in other analgesic settings
- Biological plausibility
  - Children with obstructive sleep apnea have reduced opioid requirements for analgesia*

*Brown KA et al. Anesthesiology 2004; 100:806–810.

FDA Regulatory Actions for Codeine February 2013

- Labeling Changes- all codeine-containing prescription products (pain, cough/cold)
  - Boxed Warning

WARNING: Death Related to Ultra-Rapid Metabolism of Codeine to Morphine

Respiratory depression and death have occurred in children who received codeine following tonsillectomy and/or adenoidectomy and had evidence of being ultra-rapid metabolizers of codeine due to a CYP2D6 polymorphism

  - Contraindication

Codeine sulfate is contraindicated for postoperative pain management in children who have undergone tonsillectomy and/or adenoidectomy

  - Modifications to Warnings, Pediatric Use, Patient Counseling Information sections

Genotyping Not Recommended

- Routine genotyping prior to receiving codeine was not recommended for several reasons:
  - extensive metabolizers may, in some cases, convert codeine to morphine at levels similar to ultra-rapid metabolizers.
  - the positive predictive value of the test is likely low, thus the number needed to screen in order to prevent one event is very high; and
  - genotyping may be difficult to implement because preoperative lab tests are not routinely obtained before adenotonsillectomy.

Communications

- 2nd FDA Drug Safety Communication – Feb 2013
- FDA Consumer Update
- FDA's MedWatch listserv
- New England Journal of Medicine "Perspective" piece
  - "New Evidence about an Old Drug– Risk with Codeine after Adenotonsillectomy"*
  - Coauthored with AAO-HNS

*Racoosin et al. NEJM 2013;368: 2155-2157.

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European Medicines Agency Recommendations On Codeine (June 2013)

- Use codeine-containing medicines only for acute moderate pain in children above 12 years of age
- Do not use codeine at all in children (up to 18 years) who undergo adenotonsillectomy to treat obstructive sleep apnea
- Product information should carry a warning that children with respiratory conditions should not use codeine.
- The risk of side effects with codeine may also apply to adults. Codeine should therefore not be used in any people who are known to be ultra-rapid metabolizers nor in breastfeeding mothers (because codeine can pass to the baby through breast milk).

Health Canada Recommendations On Codeine (June 2013)

- Following a review of the safety of prescription pain and cough medications containing codeine, Health Canada is no longer recommending their use in children less than 12 years of age.

Summary

- Polymorphic metabolism of codeine has resulted in fatal or life-threatening respiratory adverse events in children when taken directly or exposed through breast milk
- Evaluation in 2012 identified pain management in the post-adenotonsillectomy setting as the most well-documented setting for pediatric CYP2D6 ultra-rapid metabolizers to have adverse respiratory outcomes from codeine
  - Opioid sensitivity in children with obstructive sleep apnea may have contributed
- FDA's regulatory action in 2013 focused on preventing exposure to codeine in this sensitive group

Joint Pulmonary-Allergy Drugs and Drug Safety and Risk Management Advisory Committee Meeting

Nonprescription Codeine as an Antitussive in the Over-The-Counter (OTC) Monograph

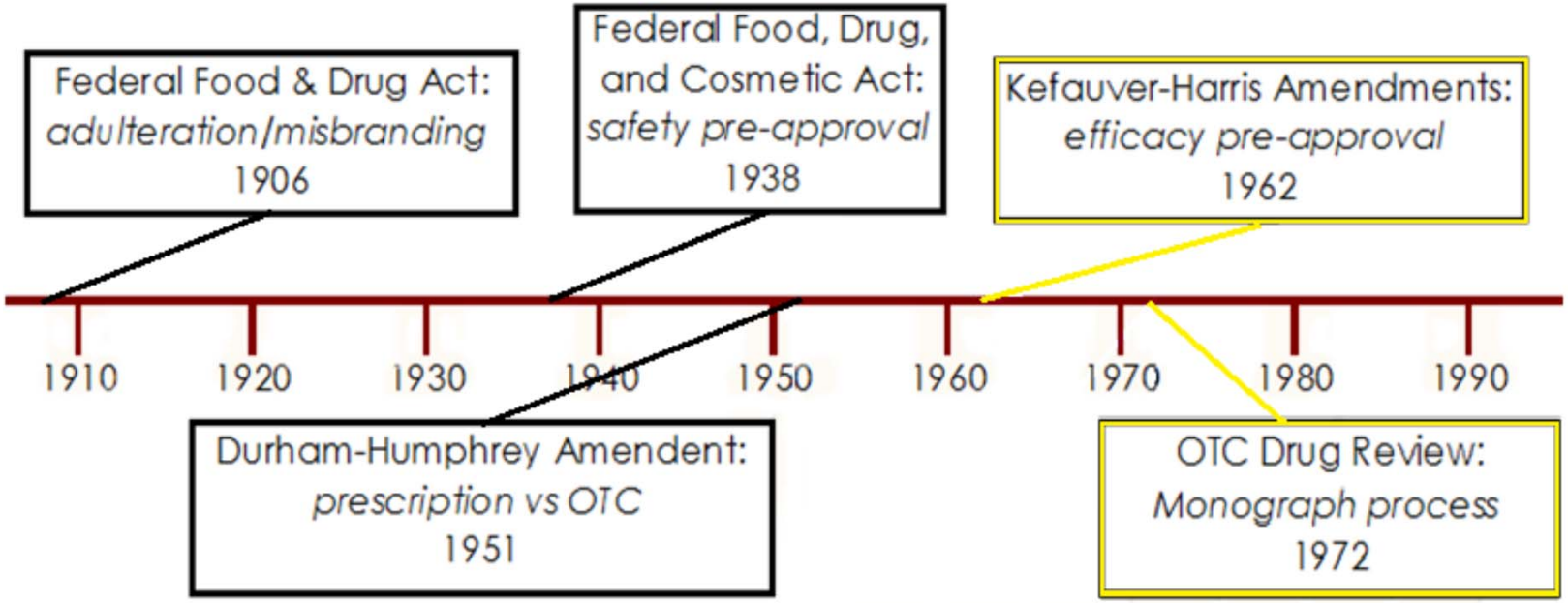
Benjamin Bishop, PharmD, MS Reg. Sci.
Division of Nonprescription Drug Products
Center for Drug Evaluation and Research
US Food and Drug Administration

Agenda

- OTC regulatory background
- History of OTC codeine
- Monograph, Federal, and State regulation
- OTC codeine availability
- Summary

OTC Drug Review & Monograph Process

- The 1962 Drug Efficacy Amendment required New Drug Applications to demonstrate **efficacy** in addition to safety
- Only 25% of a representative sample of OTC products had evidence of efficacy
- Monograph Process established for each therapeutic category



OTC Drug Review

- Advisory Review Panels were formed in 1972
  - Conducted reviews of existing data from literature and industry
  - Evaluated conditions of use for each active ingredient (dosage, indication, population, etc.)
  - Recommended a monograph for each therapeutic category
- Active ingredients were included in the monograph if they were determined to be Generally Recognized As Safe and Effective (GRASE) for OTC use.
- FDA took the recommendations and began the lengthy process of establishing the monograph in the Code of Federal Regulations

Monograph Process

Lengthy multi-step, public, notice and comment rulemaking process

- Each step is published in the *Federal Register*
- Comment may be submitted by any interested party

Comment

Comment

Advance Notice of Proposed Rulemaking

Proposed Rule (Tentative Final Monograph)

Final Rule (Final Monograph)

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- Background of OTC regulation
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Codeine in OTC Monograph

- Codeine was reviewed for inclusion in three monographs, the relevant one being the Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic (CCABA) Monograph
  - Antitussive sub-category
- The CCABA panel recommended that codeine be classified as a Generally Recognized As Safe and Effective (GRASE) antitussive for OTC use
  - In 1976, FDA issued an ANPR for the CCABA Monograph with codeine as a GRASE active ingredient
  - Comments were received both in favor and against the inclusion of codeine as a GRASE antitussive agent

Codeine in OTC Monograph

- FDA requested a recommendation from the American Academy of Pediatrics, whose response included:
  - "We believe there is a preponderance of evidence that codeine-containing cough syrups can be hazardous to young children, even in prescribed doses." {48 FR 203 (Oct. 19, 1983)}
- FDA revised the proposed label for OTC products containing codeine to state:
  - Children under 6 years of age: consult a doctor

Professional Labeling

- FDA moved the dosing instructions for children 2 to under 6 years of age to appear in professional labeling only.
- Professional labeling is labeling that provides specific information to health professionals for uses not included in OTC drug labeling.
  - Label can be provided solely to healthcare professionals
  - The product itself must be OTC-monograph compliant and may not include any of the professional labeling.
- FDA published the Tentative Final Monograph as a Proposed Rule in 1983

Codeine in OTC Monograph

- FDA revised the OTC label to state:
  - Children under 6 years of age: consult a doctor. A special measuring device should be used to give an accurate dose of this product to children under 6 years of age. Giving a higher dose than recommended by a doctor could result in serious side effects for your child.
- FDA revised the professional labeling to state:
  - "Codeine is not recommended for use in children under 2 years of age. Children under 2 years may be more susceptible to the respiratory depressant effects of codeine, including respiratory arrest, coma, and death."
- The Final Monograph was published in 1987

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Monograph Conditions for Codeine

- OTC codeine-containing products must comply with the conditions in the CCABA Final Monograph
  - Only in combination with at least one nonnarcotic active ingredient:

chlorpheniramine	phenylephrine
brompheniramine & pseudoephedrine	guaifenesin
dexbrompheniramine & pseudoephedrine	pseudoephedrine
brompheniramine & phenylephrine	guaifenesin & pseudoephedrine
chlorpheniramine & pseudoephedrine	pyrilamine
dexchlorpheniramine & phenylephrine	pseudoephedrine & pyrilamine
chlorcyclizine & pseudoephedrine	

  - Only if the nonnarcotic ingredient confers “valuable medicinal qualities other than those possessed by codeine alone.”
  - Only in concentrations of not more than:

$$\frac{\text{200 milligrams codeine}}{\text{100 milliliters or 100 grams}}$$

Monograph Conditions for Codeine

Directions in the Drug Facts Label

Adults and children 12 years of age and over:
10 to 20 milligrams every 4 to 6 hours
not to exceed 120 milligrams in 24 hours, or as directed by a doctor.

Children 6 to under 12 years of age:
5 to 10 milligrams every 4 to 6 hours,
not to exceed 60 milligrams in 24 hours, or as directed by a doctor.

Children under 6 years of age:
Consult a doctor. A special measuring device should be used to give an accurate dose of this product to children under 6 years of age.

Monograph Conditions for Codeine

Additional directions in professional labeling

Children 2 to under 6 years of age: 1 milligram per kilogram body weight per day administered in four equal divided doses. The average body weight for each age may also be used to determine dosage as follows:

Children 2 years of age (average body weight, 12 kilograms) 3 milligrams every 4 to 6 hours, not to exceed 12 milligrams in 2 hours
Children 3 years of age (average body weight, 14 kilograms) 3.5 milligrams every 4 to 6 hours, not to exceed 14 milligrams in 24 hours
Children 4 years of age (average body weight, 16 kilograms) 4 milligrams every 4 to 6 hours, not to exceed 16 milligrams in 24 hours
Children 5 years of age (average body weight, 18 kilograms) 4.5 milligrams every 4 to 6 hours, not to exceed 18 milligrams in 24 hours

Federal Regulations

- Federal regulations establish additional requirements that must be met for codeine to be sold without a prescription:
  - The purchaser's identifying information and details of the sale must be recorded and maintained
  - Maximum quantity of **240 milliliters** per purchase
  - Minimum duration of **48 hours** between purchases
  - Minimum age of **18 years** for the purchaser

State Regulation

- Individual states may prohibit the OTC sale of codeine, or they may permit it. If permitted, states may impose more stringent restrictions
- Examples:
  - A pharmacist may be required to personally perform the transaction
  - Maximum quantity of down to **60 milliliters** per purchase
  - Minimum duration of up to **96 hours** between purchases
  - Minimum age of up to **21 years** for the purchaser

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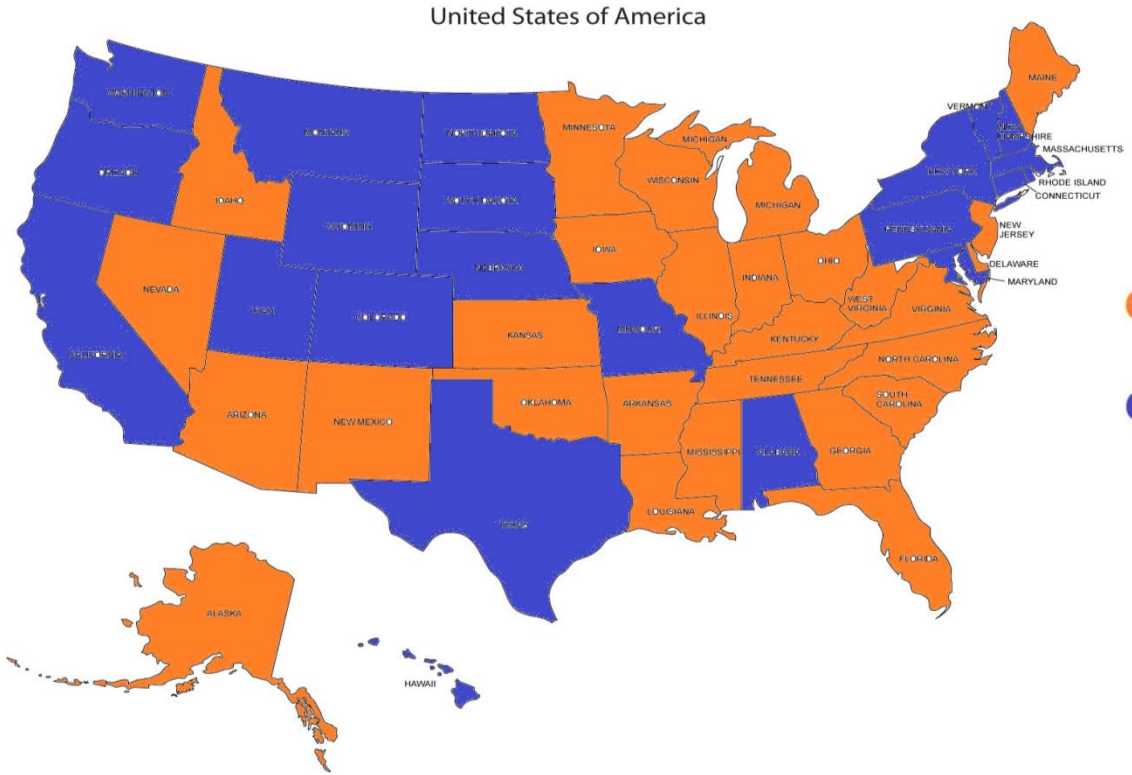
Codeine Availability

- 28 states and the District of Columbia **permit** OTC codeine sales
- 22 states and Puerto Rico **prohibit** OTC codeine sales



Codeine permitted OTC

Codeine prohibited OTC

National Association of Boards of Pharmacy
2015 Survey of Pharmacy Law

Codeine Availability

Guaifenesin AC

INACTIVE INGREDIENTS: Alcohol 3.5%, artificial cherry flavor, caramel, citric acid, disodium edetate, FD&C Red #40, glycerin, purified water, saccharin sodium, sodium benzoate, sorbitol solution.

INDICATIONS: Temporarily relieves cough due to minor throat and bronchial irritation as may occur with the common cold or inhaled irritants. Helps loosen phlegm (mucus) and thin bronchial secretions to make coughs more productive.

DIRECTIONS: Take every 4 hours or as directed by a doctor. Do not exceed 6 doses in 24 hours. **Adults and children 12 years of age and over:** Take 2 teaspoons. **Children 6 to under 12 years of age:** Give 1 teaspoon. **Children under 6 years of age: Do not use.** Giving a higher dose than recommended by a doctor could result in serious side effects for your child. Do not exceed recommended dosage.

WARNINGS: Do not take this product for persistent or chronic cough such as occurs with smoking, asthma, chronic bronchitis, or emphysema, or if cough is accompanied by excessive phlegm (mucus) unless directed by a doctor. A persistent cough may be a sign of a serious condition. If cough persists for more than 1 week, tends to recur, or is accompanied by fever, rash, or persistent headache, consult a doctor. Adults and children who have a chronic pulmonary disease or shortness of breath, or children who are taking other drugs, should not take this product unless directed by a doctor. May cause or aggravate constipation. As with any drug, if you are pregnant or nursing a baby, seek the advice of a health professional before using this product. **Keep this and all drugs out of the reach of children.** In case of accidental overdose, seek professional assistance or contact a Poison Control Center immediately.

DRUG INTERACTION PRECAUTION: Caution should be used when taking this product with sedatives, tranquilizers and drugs used for depression, especially monoamine oxidase inhibitors (MAOIs). These combinations may cause greater sedation (drowsiness) than is caused by the product used alone.

Dispense in a tight, light-resistant container as defined in the USP.

Store at controlled room temperature 20°-25°C (68°-77°F). (see USP Controlled Room Temperature) DO NOT REFRIGERATE.

OTHER INFORMATION: Each 5 mL contains: sodium 4 mg

TAMPER-EVIDENT: Do not use this product if inner foil seal over the mouth of the bottle is cut, torn, broken or missing.

BULK CONTAINER - NOT FOR HOUSEHOLD USE.

UNVARNISHED AREA

NDC 16571-302-16
TAMPER-EVIDENT
DO NOT REFRIGERATE

Guaifenesin AC Cough Syrup

(GUAIFENESIN AND CODEINE PHOSPHATE ORAL SOLUTION USP)

COUGH SUPPRESSANT • EXPECTORANT

Each teaspoon (5 mL) contains:

Guaifenesin USP	100 mg
Codeine Phosphate USP	10 mg

contains 3.5% alcohol v/v

***Under Federal law Guaifenesin AC is available without a prescription. Certain State laws may differ.**

N 3 16571 30216 1

Manufactured by:
Bio-Pharm, Incorporated Levittown, PA 19057
Distributed by: **PACK PHARMACEUTICALS, LLC**
Buffalo Grove, IL 60089 REV 08/09

TO REPORT ADVERSE DRUG EVENTS CALL:
(866) 562-4597

ONE PINT (473 mL)

PACK PHARMACEUTICALS, LLC

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Summary

- The regulatory pathway for OTC products in the monograph involves a lengthy public rulemaking process
- The FDA has established monograph requirements to regulate the sale of OTC products containing codeine indicated for antitussive use
- The Drug Facts Label for OTC products containing codeine includes directions for ages 6 and older, while directions for ages 2 to under 6 are included in professional labeling only

Thank you

Joint Pulmonary-Allergy Drugs and Drug Safety and Risk Management Advisory Committee Meeting

Clinical Considerations for the Use of Codeine as an Antitussive

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Center for Drug Evaluation and Research
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December 10, 2015

Outline

- Prescription Codeine-containing Antitussives
  - Labeling
- Clinical Considerations for use of Antitussives in Children
  - American Academy of Pediatrics
  - American College of Chest Physicians
  - FDA
  - World Health Organization
  - Health Canada
  - European Medicines Agency
  - Australian Therapeutic Goods Administration
- Alternative Antitussives
  - Prescription
  - OTC

Codeine as a Prescription Antitussive

- Immediate-release combinations (with a non-monographed antihistamine, decongestant)
  - Codeine/promethazine (1952) and Codeine/promethazine/phenylephrine (1952)
  - Codeine/triprolidine/pseudoephedrine (1960)

- Extended-release combinations – adults only
  - Codeine/chlorpheniramine polistirex extended-release suspension (2015)
  - Codeine/chlorpheniramine extended-release tablets (2015)

Relevant Labeling for Codeine Rx Antitussives

Active Ingredient	Age	Relevant Labeling
Class labeling for ALL Codeine-containing Rx analgesics and antitussives		• BOXED WARNING and WARNING regarding respiratory depression and death in infants and children due to ultra-rapid metabolism of codeine to morphine (after T&A) • CONTRAINDICATION for postoperative pain management in children post tonsillectomy and/or adenoidectomy (T&A)
Codeine-promethazine products	≥6	• CONTRAINDICATION for use in children <6 years of age • BOXED WARNING and WARNINGs regarding respiratory depression in patients <6 years due to promethazine [and the combo] • Use with caution in children ≥6 years • Dosing information: ▪ ≥12 years: 10 mg every 4 to 6 hours; NTE 60 mg in 24 hr ▪ 6 to <12 years: 5 to 10 mg every 4 to 6 hours; NTE 60 mg in 24 hr
Codeine, triprolidine, and pseudoephedrine	≥2	• Dosing information: ▪ ≥12 years: 20 mg every 4 to 6 hours; NTE 80 mg in 24 hr ▪ 6 to <12 years: 10 mg every 4 to 6 hours; NTE 40 mg in 24 hr ▪ 2 to <6 years: 5 mg every 4 to 6 hours, NTE 10 mg
Extended-release codeine-chlorpheniramine products	≥18	• Not indicated for pediatric patients <18 years of age

NTE = Not to exceed

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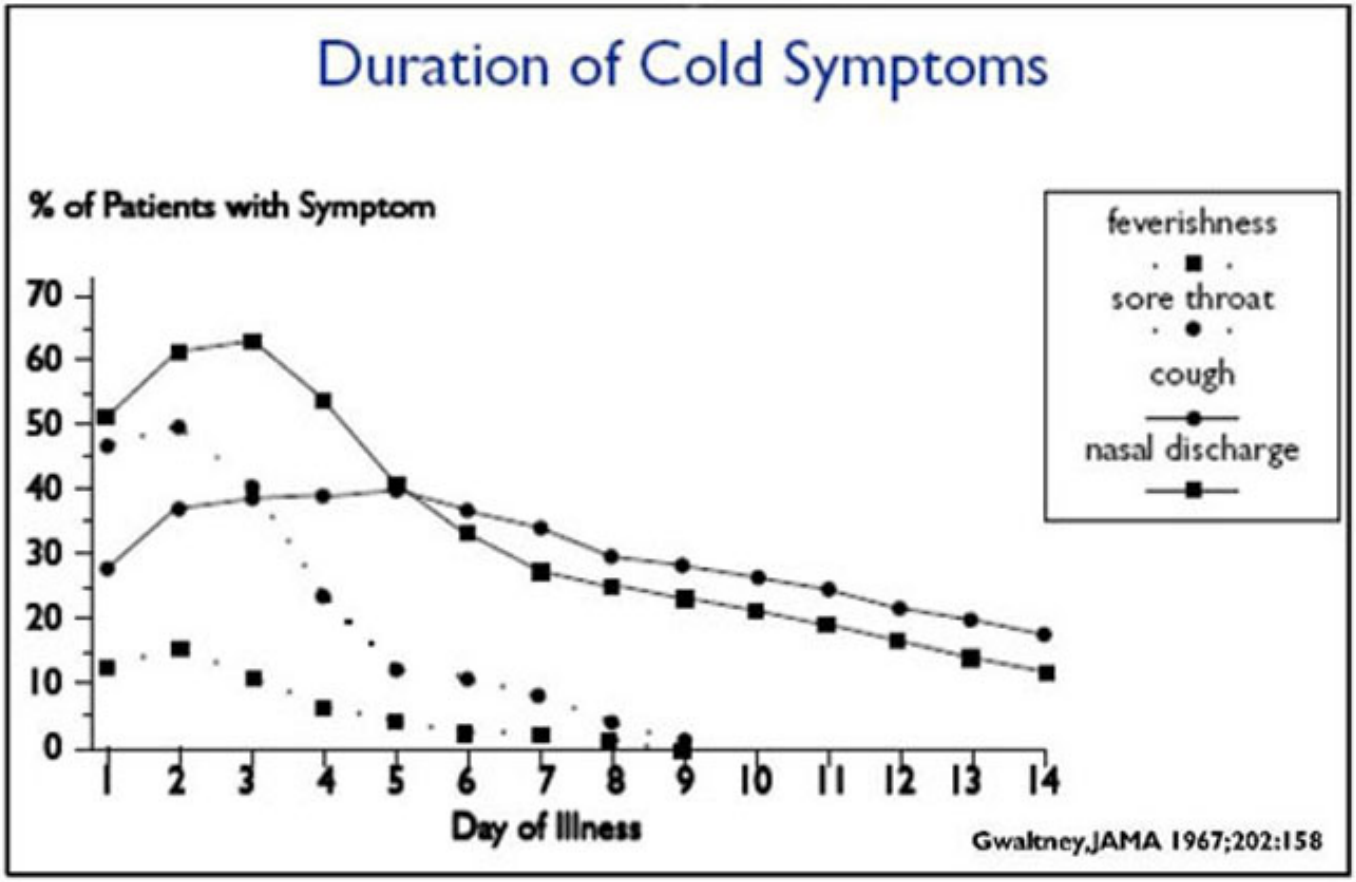
American Academy of Pediatrics (AAP)
Committee on Drugs 1997[1], reaffirmed in 10/2006[2]

- Issued a formal caution against use of antitussives, including codeine and dextromethorphan, in children
  - Acute cough is frequent, usually caused by viral infection, and self-limited; whereas treatment of chronic cough should be directed at the underlying disease
  - Suppression of cough may be hazardous
  - Adverse effects and overdosage associated with use
  - No well-controlled efficacy or safety studies
  - Dosage guidelines are derived from adults

[1] Policy Statement: Use of Codeine- and Dextromethorphan-Containing Cough Remedies in Children. *Pediatrics*. 1997;99:918–920

[2] Policy Statement: AAP Publications Retired or Reaffirmed, October 2006. *Pediatrics*. 2007;119:405



Source: http://www.cdc.gov/getsmart/community/materials-references/print-materials/hcp/adult-tract-infection.html, Accessed 11/19/2015

Corrected Attribution: Gwaltney et al., *Rhinovirus Infections in an Industrial Population*, JAMA 1967;202(6);494-500

American College of Chest Physicians, 2006*

- Issued guidelines for evaluating *chronic* cough in pediatrics
- Guidelines include the following statement:

  "In children with cough, cough suppressants and other OTC cough medications should not be used as patients, especially young children, may experience significant morbidity and mortality."

* Chang AB and Glomb WB. Guidelines for Evaluating Chronic Cough in Pediatrics. *Chest* 2006; 129 (1 Suppl):260S-283S

FDA: Advisory Committee Meeting 2007

- October 2007: Joint Nonprescription and Pediatric Advisory Committee (AC) convened to discuss the safety and efficacy of OTC cough and cold products for pediatric use
- Topics
  - Available efficacy and safety data for OTC cough/cold meds
  - Extrapolation (e.g., adult data to pediatric populations)
  - Codeine use was not a specific focus of the discussion
- The committee voted that antihistamines, nasal decongestants, and antitussives should not be used for the common cold in the following age groups:

	Should **not** be used	OK to use
Less than 2 years	21	1
2 through 5 years	13	9
6 through 11 years	7	15

Events Surrounding the 2007 AC Meeting

- October 2007: CHPA* issued a voluntary withdrawal of oral OTC cough and cold medicines that have labels that refer to “infants”
- January 2008:
  - FDA issued a public health advisory stating that children younger than 2 years should not be given cold medications because of potential serious and life-threatening side effects
  - AAP issued a statement supporting the FDA recommendation
- October 2008: CHPA announced voluntary transitioning to labeling that states “do not use” OTC oral cough and cold medicines in children under 4 years of age

* The Consumer Healthcare Products Association (CHPA) is a national trade association that represents the “leading manufacturers and distributors of OTC medicines and dietary supplements” in the United States, including cough and cold medicines.

World Health Organization (WHO)*

- March 2011: WHO removed codeine *for pain* from the list of essential medicines for children
  - Evidence indicating analgesic effect is low or absent in neonates and young children
  - Evidence of considerable pharmacogenomic variability, making its efficacy and safety questionable in an unpredictable proportion of the pediatric population
  - Low quality evidence that it is not safer or more efficacious than paracetamol [acetaminophen] or ibuprofen

* WHO guidelines on the pharmacological treatment of persisting pain in children with medical illnesses. Available at: http://whqlibdoc.who.int/publications/2012/9789241548120_Guidelines.pdf

Health Canada, 2013*

- June 2013: Health Canada announced that it had reviewed the safety of prescription codeine cough and pain medications
  - Use in children <12 years of age no longer recommended
  - Caution for use in children of all ages who have compromised respiratory function

*http://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2013/33915a-eng.php

EMA: PRAC Codeine Antitussive Assessment, 2015

- April 2014: The European Medicines Agency (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) initiated a review of the available efficacy and safety data to support use of codeine-containing products for cough in children
- Assessment Report, 2015
  - **Efficacy**: 4 published studies in children, 2 studies in adults

    Conclusion: There are no well-controlled scientific studies, and therefore, the evidence to support efficacy is limited.
  - **Safety**: Reviewed EuroVigilance data and published cases. Found 4 deaths and 10 life-threatening cases associated with use of codeine-containing products for cough/URTI.

    Conclusion: Poor metabolizers get no benefit, ultrarapid metabolizers are at high risk.

EMA: PRAC Codeine Antitussive Recommendations*

- Contraindication for use of codeine-containing products in children <12 years of age for cough and cold
- "Not recommended for use" in patients 12-18 years who have compromised respiratory function
- Contraindication for use in patients of any age who are known to be CYP2D6 ultra-rapid metabolisers
- Contraindication for all women who are breastfeeding

*http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2015/04/news_detail_002316.jsp&mid=WC0b01ac058004d5c1

*http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Codeine_containing_medicinal_products_for_the_treatment_of_cough_and_cold_in_paediatric_patients/human_referral_prac_000039.jsp&mid=WC0b01ac05805c516f

Australian Therapeutic Goods Administration (TGA)

- July 2015: Advisory Committee on the Safety of Medicines meeting
- October 2015: Published the results of a pharmacovigilance and special access branch safety review. While they found no Australian cases, they nevertheless recommended:

1. Use of codeine in children younger than 12 years of age for any indication should be contraindicated.
2. Use of codeine in children aged 12-18 years should be contraindicated post adeno-tonsillectomy for obstructive sleep apnoea.
3. Existing warnings contraindicating codeine use by breastfeeding mothers should be made consistent across all codeine-containing products, and warnings should be added to advise against using codeine if known to be an ultra-rapid metaboliser.
4. Health professionals, patients and caregivers should be educated regarding the variability of codeine efficacy, the possibility of ultra-rapid metabolism-related morphine overdose and the signs of such, including respiratory depression.

Regulatory Agency Actions/Recommendations

Agency	Analgesia	Cough
Australian Therapeutic Goods Administration	Contraindicated <12 years of age Contraindicated for children (all ages) post adeno-tonsillectomy	Contraindicated <12 years of age
European Medicines Agency	Contraindicated <18 years of age undergoing tonsillectomy and/or adenoidectomy for obstructive sleep apnea Only use in children >12 years of age	Contraindicated <12 years of age Not recommended in children/adolescents 12-18 years who have breathing problems
Health Canada	Not recommended <12 years of age Caution for children (all ages) with compromised respiratory function	Not recommended <12 years of age Caution for children (all ages) with compromised respiratory function
Food and Drug Administration	Contraindicated for children (all ages) post-operative pain management post tonsillectomy and/or adenoidectomy	

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Alternative Prescription Antitussives

- Non-narcotic
  - Benzonatate (perles and capsules)

- Narcotic
  - Hydrocodone/Homatropine
  - Hydrocodone immediate- and extended-release combinations with chlorpheniramine, pseudoephedrine, and/or guaifenesin

Benzonatate

- Peripheral anesthetic acts by anesthetizing the stretch receptors located in the respiratory passages, lungs, and pleura
- Approved for use in adults and children ≥10 years

  "Safety and effectiveness in children below the age of 10 have not been established."
- Perles/capsules – WARNING re safety concerns if sucked or chewed

  "Severe hypersensitivity reactions (including bronchospasm, laryngospasm and cardiovascular collapse) have been reported which are possibly related to local anesthesia from sucking or chewing the capsule instead of swallowing it. Severe reactions have required intervention with vasopressor agents and supportive measures."
- Overdose has resulted in death
- Accidental ingestion resulting in death has been reported in children <10 years

Hydrocodone-containing Antitussives

- Centrally-acting opioid
- With homatropine
  - Dosing information for adults and children ≥6 years of age
  - WARNING about respiratory depression in patients <6 years
  - Pediatric Use: Use with caution in children ≥6 years
- Extended-release combination (with chlorpheniramine)
  - CONTRAINDICATION for use in patients <6 years because use is associated with cases of fatal respiratory depression
- Immediate-release combinations
  - NOT indicated for pediatric patients <18 years of age
  - WARNING regarding respiratory depression, including fatalities, in children <6 years

Relevant Labeling for Alternative Rx Antitussives

Active Ingredient	Class	Age	Relevant Labeling
Benzonatate	Peripheral Anesthetic	≥10y	• Soft capsules: Bronchospasm, laryngospasm and cardiovascular collapse have been reported after sucking or chewing on capsules • Accidental ingestion resulting in death has been reported in children <10 years • Overdose has resulted in death
Hydrocodone + homatropine + chlorpheniramine (extended-release)	Centrally acting opioid	≥6y	• With Homatropine: WARNING about respiratory depression in patients <6 years • Use with caution in children ≥6 years • Extended-release: CONTRAINDICATION in patients <6 years because use is associated with cases of fatal respiratory depression
Hydrocodone + chlorpheniramine + pseudoephedrine (PSE) + chlorpheniramine & PSE + guaifenesin + guaifenesin & PSE	Centrally acting opioid	≥18y	• Not indicated for pediatric patients <18 years • WARNING regarding respiratory depression, including fatalities in children <6 years

OTC Antitussives: Centrally Acting

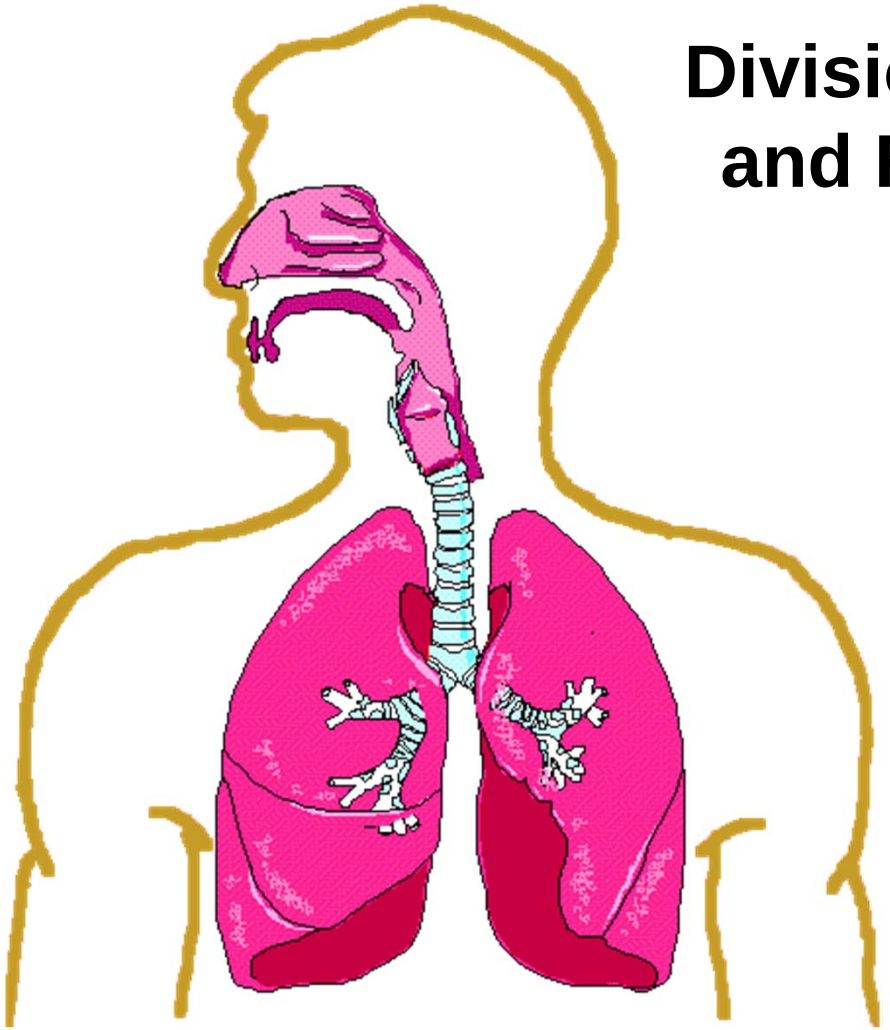
Active Ingredient	Class	Age	Relevant Labeling
Chlophedianol	Non-narcotic	≥6y	• Non-narcotic for temporary relief of cough • Do not take for chronic cough • Children under 6 years: Consult a doctor • OTC monograph contains professional labeling for dosing in children 2 to <6 years
Dextromethorphan	Non-narcotic	≥2y	• Non-narcotic for temporary relief of cough • Do not take for chronic cough • Children under 2 years: Consult a doctor
Diphenhydramine	Antihistamine /antitussive	≥6y	• Non-narcotic for temporary relief of cough • May cause marked drowsiness • Alcohol, sedatives, and tranquilizers may increase sedative effect • Do not give to children <12 years of age who have a breathing problem • Children under 6 years: Consult a doctor • OTC monograph contains professional labeling for dosing in children 2 to <6 years

OTC Antitussives: Topical

Active Ingredient	Class	Age	Relevant Labeling
Camphor and Menthol	Topical (ointment, lozenge, steam inhalation)	≥2y	• Topical: For external use only • Flammability: Safety concern about fire-related events when ointment vehicle or alcohol-based solutions are placed in hot water or heated in the microwave • Children <2 years: Consult a doctor

Summary

- Codeine-containing Rx antitussive products are available in combination with other medications, such as antihistamines and decongestants
- Professional societies have voiced significant concerns for the use of all cough medicines in children, including codeine
- Health Canada, the European Medicines Agency, and the Australian Therapeutic Goods Administration have recently singled out codeine-containing antitussives as a safety risk in children, including contraindicating their use in children less than 12 years of age
- Prescription and non-prescription alternatives to codeine for cough also have risks



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Joint Meeting of the Pulmonary-Allergy Drugs Advisory Committee (PADAC) and the Drug Safety and Risk Management Advisory Committee (DSaRM)

December 10, 2015

Pediatric Post-Marketing Utilization, Pharmacovigilance, Epidemiological Data on Codeine-Containing Products

Drug Utilization Patterns of Codeine-Containing Products 2010-2014

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Outline

- Sales distribution of codeine products
- Over the counter (OTC) retail sales of cough/cold codeine products
- Pediatric utilization of prescription codeine products
- Limitations
- Summary

Classification of Codeine Products

- Analgesic versus cough/cold codeine
  - Products are grouped based on active ingredients
  - Examples:
    - Analgesic: single-ingredient codeine and combination codeine-acetaminophen
    - Cough/Cold: combination codeine-guaifenesin and codeine-promethazine

Sales Distribution

2014

IMS Health, National Sales Perspectives™

U.S. Sales Distribution

National estimates of bottles/packages of all codeine-containing products sold from manufacturers to retail and non-retail channels of distribution in U.S.**

	Year 2014		
Product	**Outpatient Retail**	**Mail Order/ Specialty**	**Non-Retail**
All codeine products	**65%**	**<1%**	**34%**

- **Outpatient Retail Channel:**
  - Over-the-counter sales: cough/cold codeine-containing products
  - Retail pharmacy prescription use: analgesic and cough/cold products

Source: IMS Health, National Sales Perspectives™. Year 2014. Data extracted August 2015.

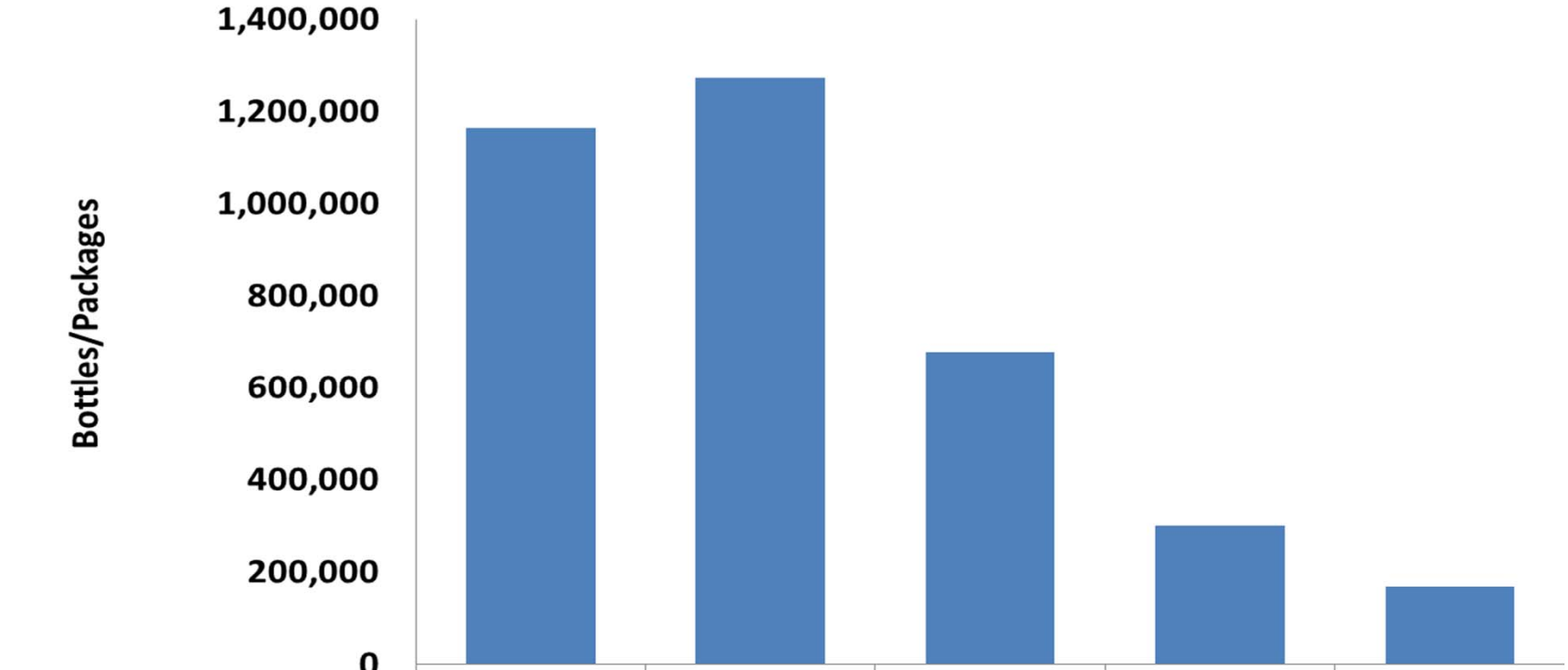
**An example is a 120mL bottle containing combination codeine-guaifenesin.

U.S. OTC Retail Sales

2010-2014

IMS Health, OTC International Market Tracking Database

U.S. OTC Retail Sales



	2010	2011	2012	2013	2014
Total OTC Retail Sales	1,165,094	1,272,621	678,730	301,294	169,300

National estimates of bottles/packages of cough/cold codeine-containing products sold over-the-counter to the consumers from U.S. retail store outlets

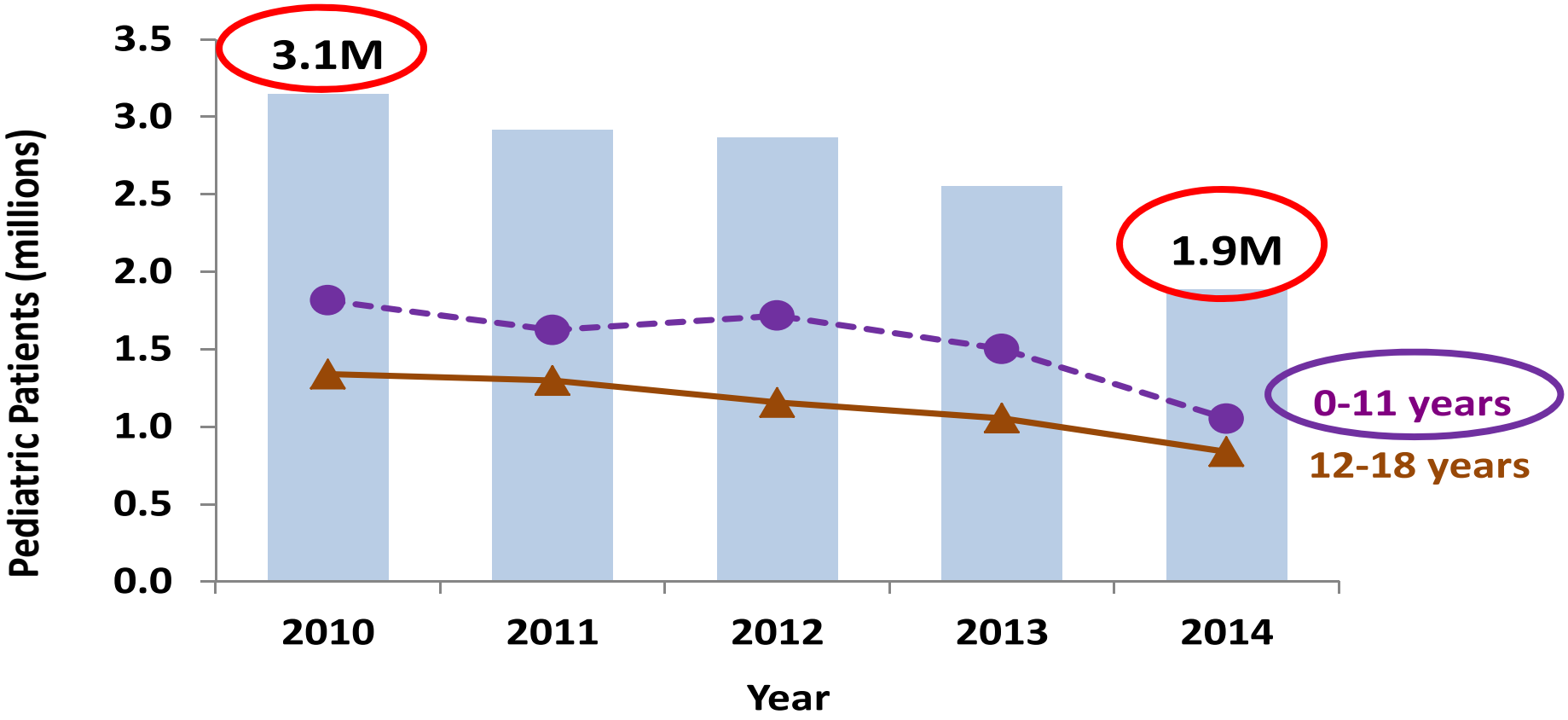
Source: IMS Health, OTC International Market Tracking. Years 2010-2014. Data extracted July 2015.

U.S. Pediatric Outpatient Retail Utilization

2010-2014

IMS Health, Vector One®: Total Patient Tracker Database

Total Codeine: Pediatric Use (0-18 years)

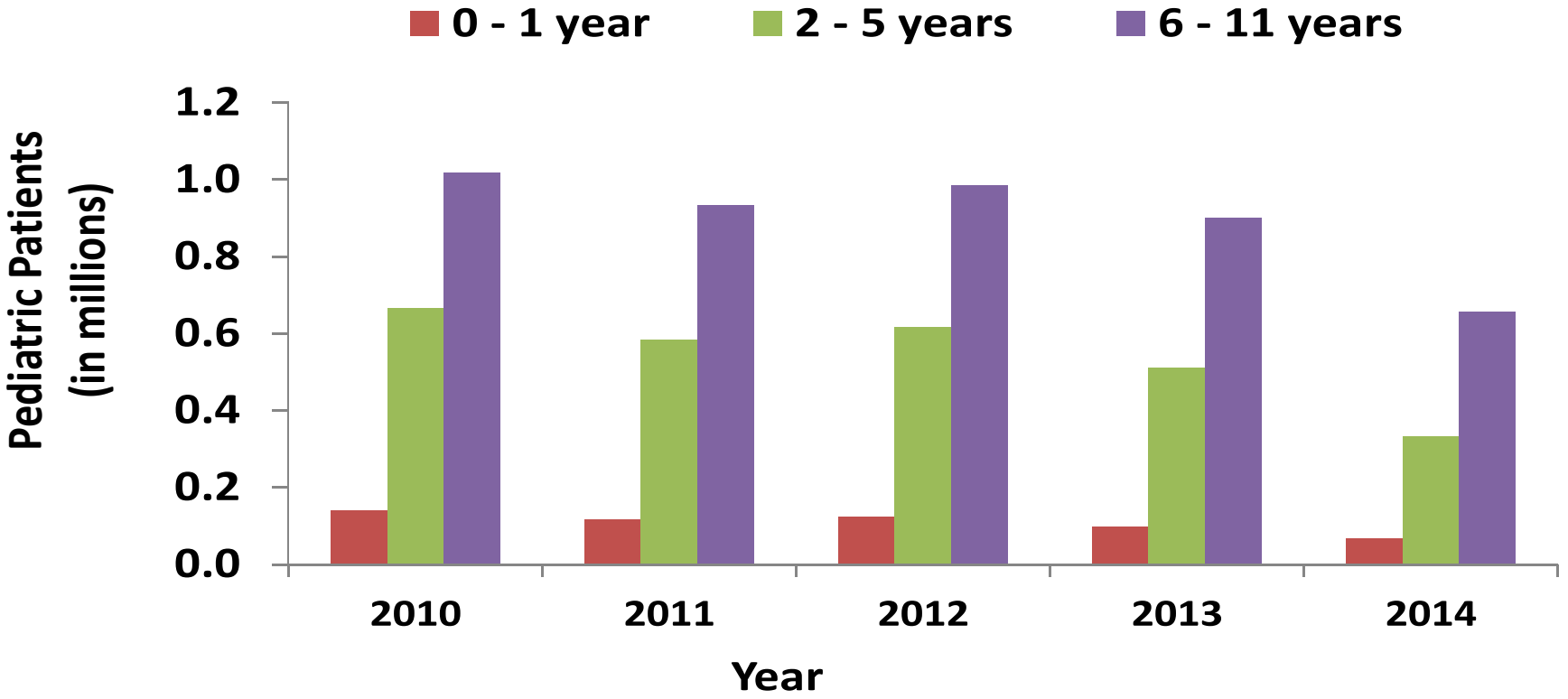


National estimates of total pediatric patients (0-18 years*) who received dispensed prescriptions for codeine-containing products from U.S. outpatient retail pharmacies

*Patient age groups are inclusive of all patients up to the day before their next birthday. For example, patients aged 0 - 16 years includes patients aged 16 years and 11 months.

Source: IMS Health, Vector One®: Total Patient Tracker. Years 2010 through 2014. Data extracted June 2015.

Total Codeine: Pediatric Use (0-11 years)



National estimates of pediatric patients (0-11 years*) who received dispensed prescriptions for codeine-containing products from U.S. outpatient retail pharmacies

*Patient age groups are inclusive of all patients up to the day before their next birthday. For example, patients aged 0 - 16 years includes patients aged 16 years and 11 months.

Source: IMS Health, Vector One®: Total Patient Tracker. Years 2010 through 2014. Data extracted June 2015.

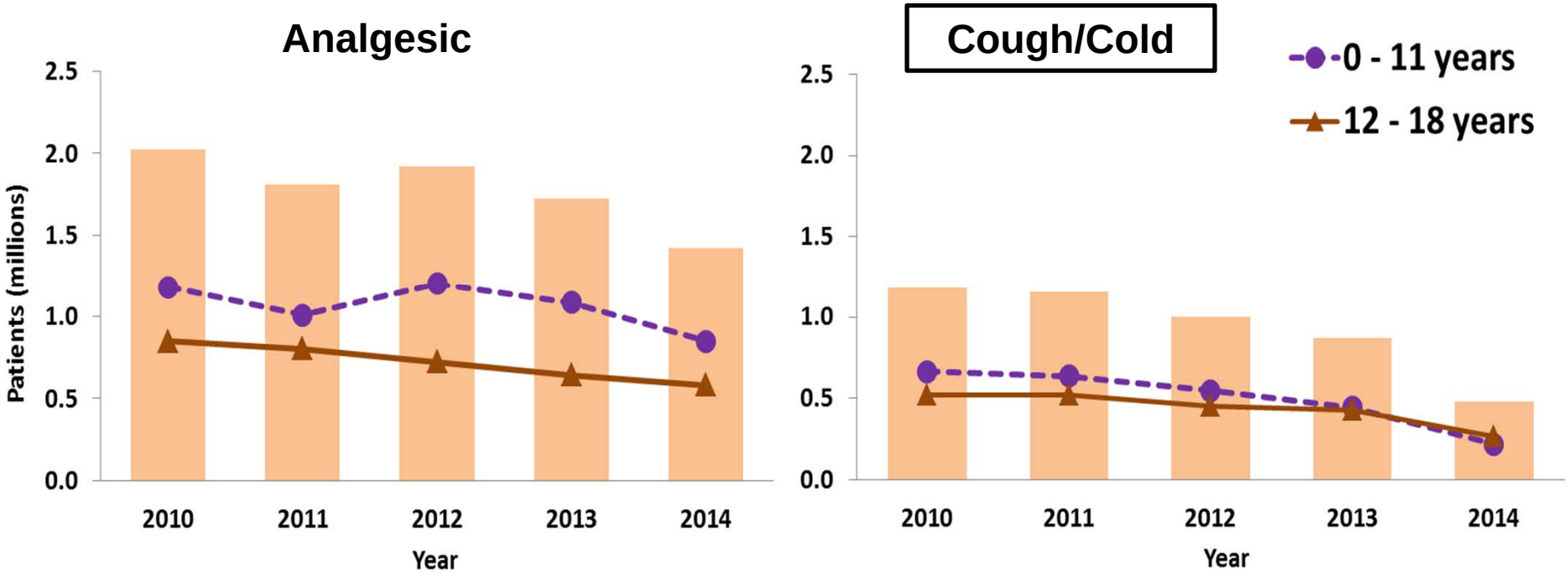
Pediatric Use by Active Ingredient

From 2010-2014:

- **Analgesic codeine**
  - Codeine-Acetaminophen: >99% of pediatric patients, annually
  - Single-ingredient codeine: <1% of pediatric patients, annually
- **Cough/Cold codeine**
  - Codeine-Guaifenesin: ranged from 52%-64% of pediatric patients, annually
  - Codeine-Promethazine: ranged from 31%-42% of pediatric patients, annually

Source: IMS Health, Vector One®: Total Patient Tracker. Years 2010 through 2014. Data extracted June 2015.

Pediatric Use: Analgesic and Cough/Cold



National estimates of pediatric patients* who received dispensed prescriptions for analgesic or cough/cold codeine-containing products from U.S. outpatient retail pharmacies

*Patient age groups are inclusive of all patients up to the day before their next birthday. For example, patients aged 0 - 16 years includes patients aged 16 years and 11 months.

Source: IMS Health, Vector One®: Total Patient Tracker. Years 2010 through 2014. Data extracted June 2015.

Limitations

- OTC retail sales data
  - No information on patient demographic or direct patient use
- Outpatient retail pharmacy data
  - Analyses not generalizable to other settings of care; e.g. hospitals or mail-order/specialty setting
  - No linkage between a dispensed prescription and a diagnosis

Summary

- Decline in OTC retail sales of cough/cold codeine
- Decline in pediatric use of prescription codeine (analgesic or cough/cold) from outpatient retail setting
  - Majority of pediatric patients were 12 years and younger
  - Majority of pediatric patients received combination codeine-acetaminophen
- In 2014, approximately 1.9 million pediatric patients received prescription codeine products

Postmarketing Safety Data on Codeine-Containing Products

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US Food and Drug Administration

Outline

- FDA Adverse Event Reporting System (FAERS) Overview
- Respiratory Depression in the Pediatric Population with Codeine-containing products
  - Case Reports from FAERS and Medical Literature
- Summary

FDA Adverse Event Reporting System (FAERS)

FAERS Strengths

- Computerized database
- > 11 million reports since 1969
- Includes all U.S. marketed products
- Includes all uses (both approved and off-label use)
- Includes broad patient populations
- Detection of events not seen in clinical trials
- Detection of events with rare background rate
- Identification of reporting trends, possible risk factors, at risk populations, and other clinically important emerging safety concerns

FAERS Limitations

- Causal relationship between a product and event is not required for reporting to the FDA
- Quality of reports is variable – information is limited in some reports
- Under-reporting – not every adverse event is reported
- FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population

Search Strategy for Pediatric Cases of Respiratory Depression

- FAERS database
  - All codeine-containing products
  - Time period: through May 26, 2015
  - Age range: 18 years of age and below
  - Serious outcome: death, life-threatening events, hospitalization, disability, congenital anomaly, other serious important medical events

- Medical literature case reports
  - Time period: June 1, 2012 – July 15, 2015

Case Definition for Respiratory Depression

- Temporal association following codeine-containing product administration

AND one of the following:

- Signs or symptoms consistent with respiratory depression such as slow or shallow breathing, difficult or noisy breathing, or unusual sleepiness
- Naloxone administration
- A diagnosis of respiratory depression
- Death outcome without a clear alternative reason

Descriptive Characteristics of Serious Pediatric FAERS Cases of Respiratory Depression (N = 64)	
Age (n = 64)	0-1 year (16), 2-5 years (23), 6-11 years (11), 12-18 years (14)
Codeine-Containing Products (n = 65)*	Acetaminophen/codeine (26), Codeine unspecified (23), Promethazine/codeine/phenylephrine (5), Promethazine/codeine (5), Guaifenesin/codeine (2), Chlorpheniramine/phenylephrine/dihydrocodeine (1), Triprolidine/pseudoephedrine/codeine (1), Aspirin/codeine (1), Dihydrocodeine unspecified (1)
Time to AE Onset from Start of Therapy (n = 31)	1 dose (10), 2 doses (5). 3 doses (4), 4 doses (3), 6 doses (3), 10 doses (1), 12 doses (3). 18 doses (2)
Mention of CYP2D6 Genotype (n = 10)	Extensive metabolizer (3) Ultra-rapid metabolizer (7)
Reasons for Use (n = 48)	Pain (34), Cough and Cold (14)

* Cases may contain more than one codeine-containing product

Descriptive Characteristics of Serious Pediatric FAERS Cases of Respiratory Depression for Analgesic Use (N = 34)	
Age (n = 34)	0-1 year (3), 2-5 years (13), 6-11 years (10), 12-18 years (8)
Country (n = 34)	United States (20), Foreign (14)
Codeine-Containing Products (n = 35)*	Acetaminophen/codeine (21) Codeine unspecified (13) Promethazine/codeine (1)
Serious outcomes† (n = 22)	Death (14), Hospitalization (10), Life-threatening (13), Disability (1), Other Serious (15)

*Cases may contain more than one codeine-containing product
† Cases may contain multiple outcomes

Descriptive Characteristics of Serious Pediatric FAERS Cases of Respiratory Depression for Cough/Cold Use (N = 14)	
Age (n = 14)	0-1 year (6), 2-5 years (7), 6-11 years (1)
Country (n = 14)	United States (11), Foreign (3)
Codeine-Containing Products (n = 16)*	Promethazine/codeine/phenylephrine (4) Promethazine/codeine (3) Codeine unspecified (3) Guaifenesin/codeine (2) Chlorpheniramine/phenylephrine/dihydrocodeine (1) Triprolidine/pseudoephedrine/codeine (1) Aspirin/codeine (1) Dihydrocodeine unspecified (1)
Serious outcomes† (n = 22)	Death (7), Hospitalization (7), Life-threatening (2), Disability (1), Other Serious (5)

*Cases may contain more than one codeine-containing product

† Cases may contain multiple outcomes

Serious Pediatric FAERS Cases of Respiratory Depression with Codeine-containing Products by Outcome, through May 26, 2015 (N=64)

	Death Outcome	Non-Fatal Outcomes*
Pediatrics (0-18 years)	24	69
< 6 years old	17	42
6 to < 12 years old	4	14
12 to < 18 years old	3	13

*Non-fatal outcomes may include one or more of the following: life-threatening events, hospitalization, disability, congenital anomaly or other serious important medical events

Pediatric Death Cases (n = 24): Reasons for Use

Reason for Use	0 to <12 Years of Age (n = 21)	12-18 Years of Age (n = 3)
Cough and Cold	7	0
Post tonsillectomy and/or adenoidectomy	6	1
General Pain	2	0
Postoperative pain unrelated to tonsillectomy/adenoidectomy	2	0
Sore throat/strep pain	1	1
Dental pain	0	1
Unknown reason for use	3	0

Case Reports

Medical Literature Case Reports

- 2013 Friedrichsdorf et al. (Journal of Opioid Management) – "Codeine-associated pediatric deaths despite using recommended dosing guidelines: Three case reports"
  - Reason for use of codeine-containing products: pain management post tonsillectomy and/or adenoidectomy, other postoperative pain management, cough and cold
  - All three children were overweight or obese; however, the **codeine doses were within recommended dose ranges** for adjusted lean weight
  - Two of the case reports were reported in FAERS

Friedrichsdorf SJ, Postier Nugent A, Stobl A. Codeine-associated pediatric deaths despite using recommended dosing guidelines: Three case reports. Journal of Opioid Management, Mar-April 2013; 9(2): 151-155.

Death Case Report 1*: Postoperative pain management unrelated to tonsillectomy and/or adenoidectomy

- 10-year-old overweight female of Guatemalan descent underwent orthopedic surgery and discharged home 5 days postop
- Found un-responsive following treatment with acetaminophen with codeine 20-40mg of codeine (total of 2 doses) and diazepam 2-4mg (1 dose)
- Postmortem codeine and morphine blood concentrations were in the toxic range
- Past medical history includes cerebral palsy and reactive airway disease. Preoperative examination noted a history of snoring and enlarged tonsils

* This case was reported both in FAERS and as part of a case series by Friedrichsdorf et al.

Death Case Report 2*: Pain Management post tonsillectomy and/or adenoidectomy

- 4-year-old obese female status post tonsillectomy/adenoidectomy discharged home with acetaminophen with codeine every 4 hours for pain
- She received a total of 4 doses at 4-hour intervals, went to bed, and was found unresponsive the following morning
- Resuscitative measures were unsuccessful
- CYP2D6 testing found the patient to have an extensive metabolizer (normal) phenotype

* This case was part of a case series by Friderichsdorf et al.

Death Case Report 3*: Cough and Cold

- 6-year-old overweight female was prescribed guaifenesin with codeine (10-20mg of codeine) for severe cough and respiratory infection
- She received a total of 3 doses throughout the day and was found dead the next morning by her mother
- Postmortem codeine and morphine blood concentrations were in the toxic range

* This case was reported both in FAERS and as part of a case series by Friedrichsdorf et al.

Non-fatal FAERS Case: Pain management unrelated to tonsillectomy and/or adenoidectomy

- 13-year-old female of African American descent took acetaminophen with codeine (30mg) for sickle cell pain management
- After 1 dose, the patient's mother noted that she had extreme drowsiness and was difficult to arouse
- Genetic testing showed the patient to be a CYP2D6 ultra-rapid metabolizer
- Patient had previously taken acetaminophen with codeine and experienced drowsiness at that time as well

Summary

- There is case report evidence of respiratory depression, sometimes resulting in death, following codeine-containing product use
  - Pediatric case series primarily involved children less than 12 years of age
- Respiratory depression after codeine-containing product exposure occurred when the products were used not only for pain management following tonsillectomy and/or adenoidectomy, but also for other pain management and for cold/cough management
- CYP2D6 genotyping is not reliably predictive of outcome

Epidemiologic Data on Pediatric Emergency Department Visits Associated with Codeine-Containing Cough/Cold and Analgesic Products

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Outline

- **Drug Abuse Warning Network**
  - Background/Methods
  - Findings
  - Strengths/Limitations
  - Conclusions
- **NEISS-CADES**
  - Background/Methods
  - Findings
  - Strengths/Limitations
  - Conclusions

Drug Abuse Warning Network (DAWN)

- Administered by the Substance Abuse and Mental Health Services Administration (SAMHSA)
- Data are available 2004-2011
- Data from a stratified probability sample of 233 hospitals
- Published national estimates of drug-related emergency department (ED) visits by drug substance and by case type.
  - Adverse Drug Reaction (ADR): allergic reactions, drug interactions, side effect of drug

DAWN 2004-2011: National Estimates of ADR ED Visits by Age Group for Codeine-Containing Analgesic Products

Age Band	2004	2005	2006	2007	2008	2009	2010	2011
0-5 years	*	*	*	*	542	853	*	*
95% CI					(106–979)	(233-1,474)	*	*
6-11 years	*	846	822	1,207	1,060	1,342	*	*
95% CI	*	(328-1,364)	(120-1,524)	(202-2,213)	(524 -1,597)	(460-2,223)	*	*
12-17 years	841	653	1,520	984	609	1,707	1,043	1,073
95% CI	(184 -1,498)	(145-1,161)	(781-2,259)	(439-1,530)	(220-998)	(734 -2,679)	(398 -1,688)	(123 -2,023)

* indicates figure does not meet SAMHSA's standards of precision for publication
Source: Center for Behavioral Health Statistics and Quality, SAMHSA, Drug Abuse Warning Network, 2011

DAWN: Strengths and Limitations

+ Public health surveillance system
+ Nationally representative sample
+ Large number of hospitals
+ Provides national estimates

– Data limited to 2004-2011
– Do not provide clinical details on ED visit
– ADR category too broad
– No information on events resulting in deaths

Summary of DAWN Findings

- National estimates for pediatric adverse drug reaction ED visits were not available for codeine-containing cough and cold products
- DAWN data show there were pediatric adverse drug reaction ED visits associated with codeine-containing analgesic products in 2004-2011

National Electronic Injury Surveillance System – Cooperative Adverse Drug Event Surveillance (NEISS-CADES)

- Joint effort of the CDC, the U.S. Consumer Product Safety Commission and the FDA
- Data are currently available for 2004-2013.
- Data from a stratified sample of 63 hospitals
- Data only on patients alive at time of discharge, i.e. no deaths.
- Only **counts** are presented; national estimates were too imprecise
- ADE Mechanism:
  - Accidental/unintentional
  - Allergic reaction
  - Adverse effect

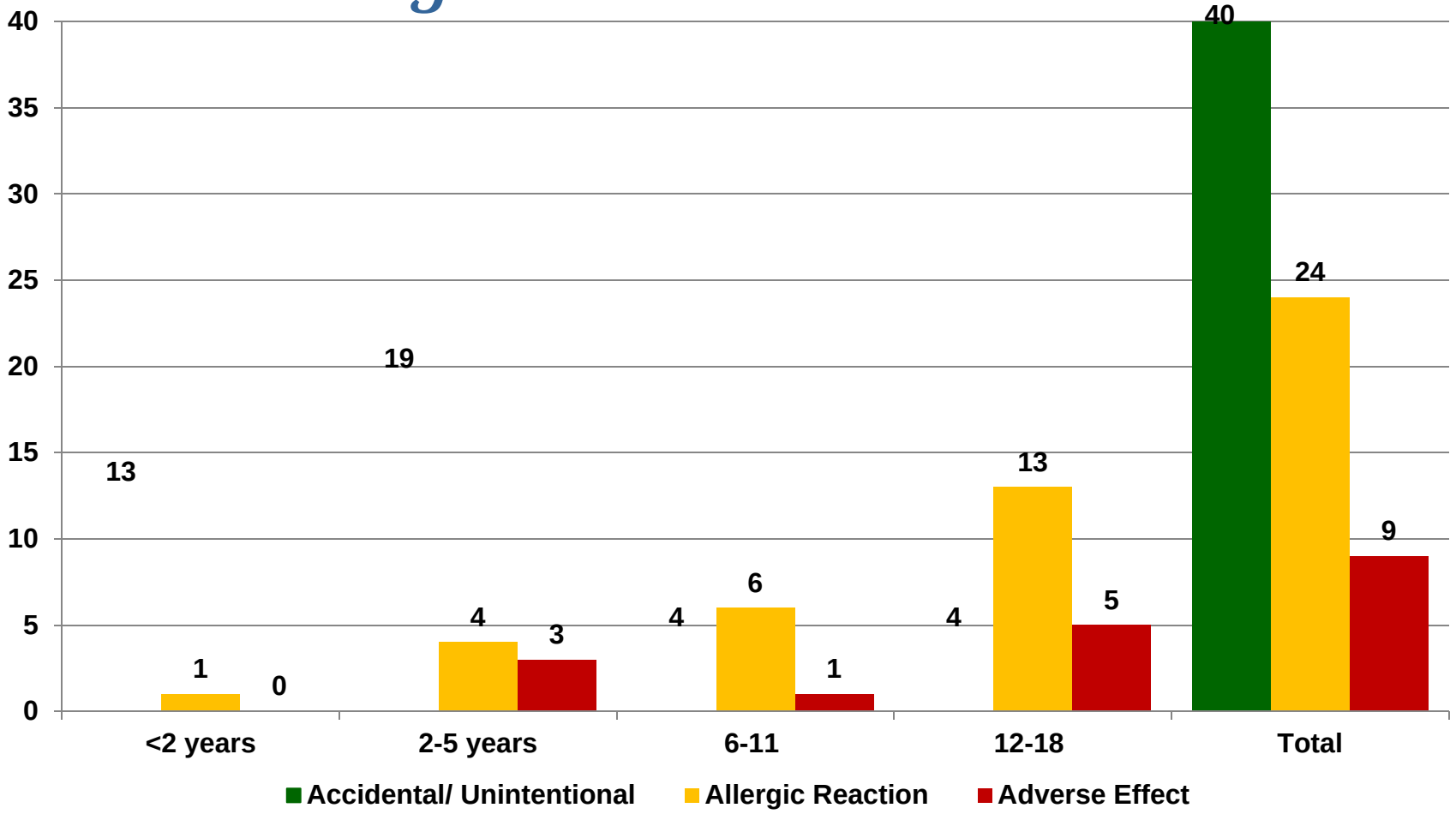
NEISS-CADES 2004-2013: Pediatric ED Visits by Drug Category for Codeine-Containing Products

	Cough and Cold	Analgesics
2004	7	21
2005	5	33
2006	6	32
2007	6	28
2008	9	28
2009	6	33
2010	7	21
2011	5	22
2012	14	33
2013	8	10
Total	**73**	**261**

Note: These are counts of ED visits from a sample of 63 hospitals, they are not national estimates

Source: National Electronic Injury Surveillance System – Cooperative Adverse Drug Event Surveillance 2004- 2013 (NEISS-CADES)

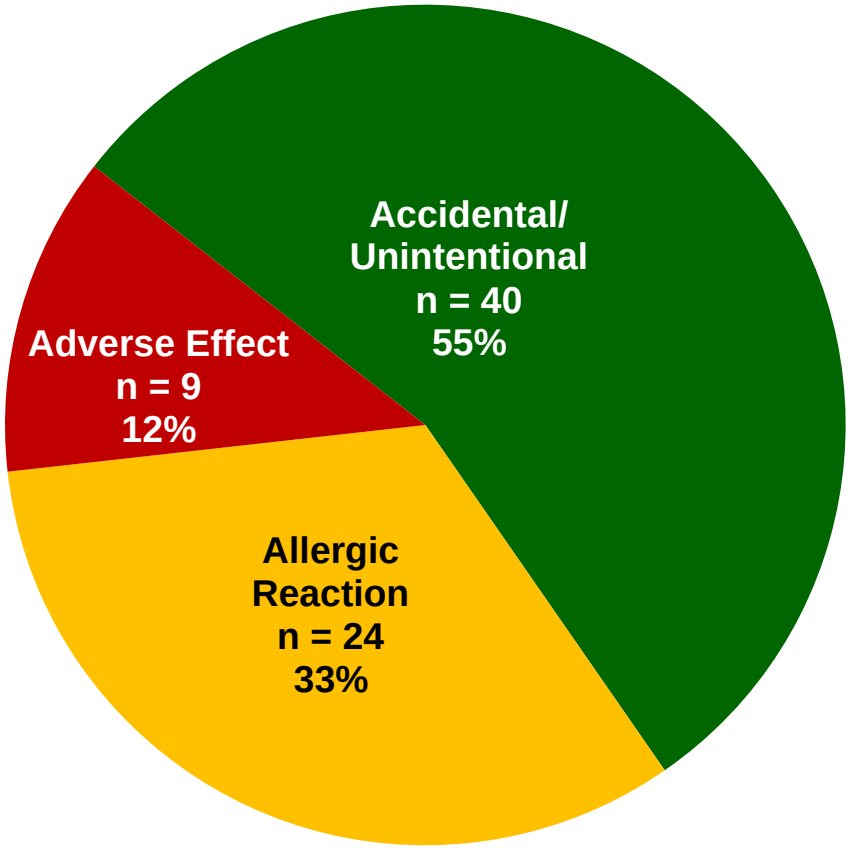
NEISS-CADES 2004-2013: ED Visits by Adverse Event and Age Group for *Cough and Cold Products*



Source: NEISS-CADES 2004- 2013

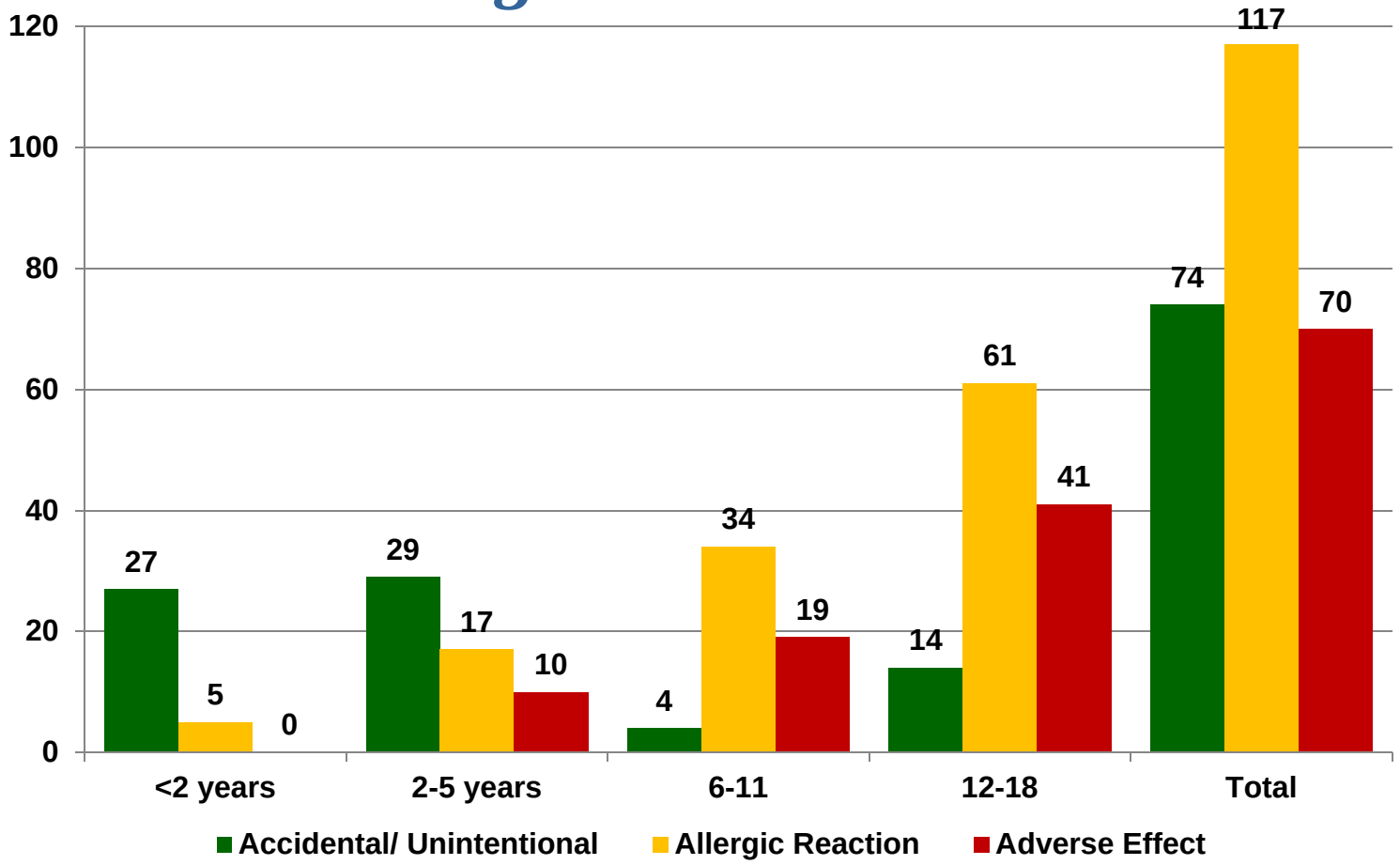
NEISS-CADES 2004-2013: Pediatric ED Visits by Type of ADE Mechanism for Cough and Cold Products

ADE Symptoms	Number of Events
Respiratory Depression Related	
Dyspnea	1
Somnolence	1
Other Symptoms	
Gastro-intestinal Events	3
Dizziness/syncope	2
Dystonia	1
Visual Hallucination	1
Total Number of listed Symptoms	9



Source: NEISS-CADES 2004-2013

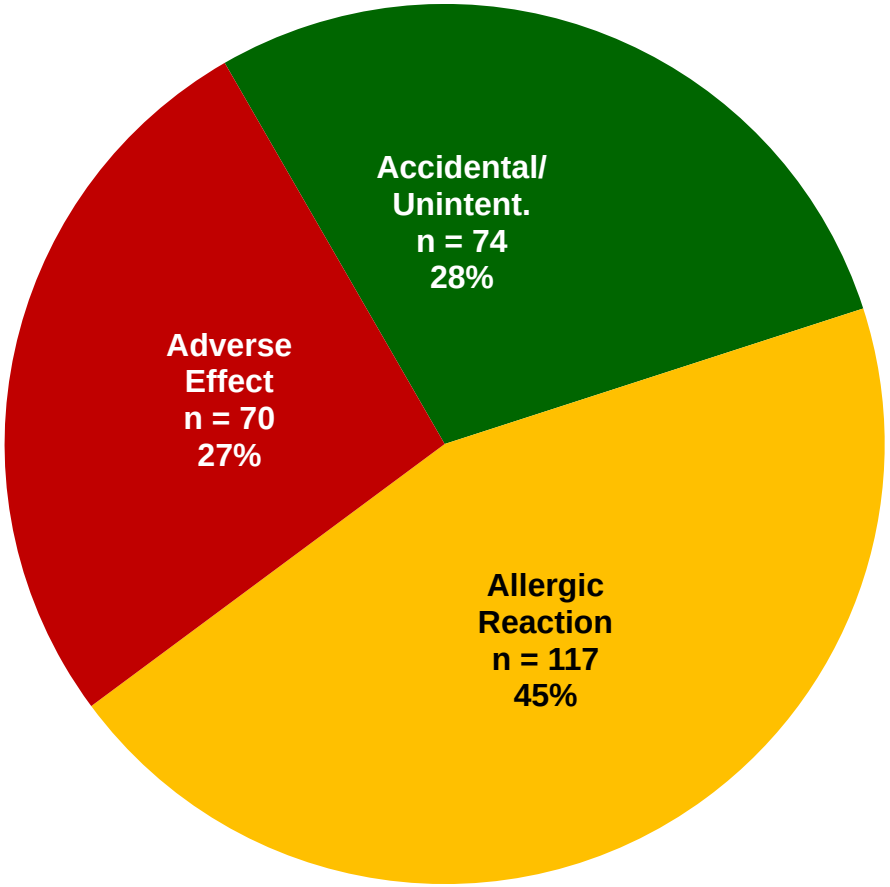
NEISS-CADES 2004-2013: ED Visits by Adverse Event and Age Group for *Analgesic Products*



Source: NEISS-CADES 2004-2013

NEISS-CADES 2004-2013: Pediatric ED Visits by Type of ADE Mechanism for Analgesic Products

ADE Symptoms	Number of Events
Respiratory Depression Related	
Dyspnea	8
Somnolence/sedation	3
Respiration Abnormal/Decreased	2
Other Symptoms	
Gastro-Intestinal Events	80
Dizziness/syncope/presyncope/fall	10
Cardiac Complaints	9
Physical complaints/discomfort	11
Abnormal Behavior/ALOC*	7
Total Number of listed Symptoms	**130**



ALOC = altered level of consciousness

Source: NEISS-CADES 2004-2013

NEISS-CADES: Strengths and Limitations

+ Active surveillance system
+ Nationally representative sample
+ Provides clinical detail on the ED visit

– Limited to 63 hospitals
– Counts too low to generate national estimates
– Does not provide information on deaths

Summary of NEISS-CADES Findings

- Pediatric ED visits related to both codeine-containing **cough and cold** and **analgesic** products were found
  - Accidental/unintentional ingestions accounted for the largest proportion of ED visits related to **cough and cold** products,
  - Allergic reactions accounted for the largest proportion ED visits related to **analgesic** products.
- ED visits that may be precursors to respiratory depression were found in both drug categories

Summary of Key Findings

- Both DAWN (2004-2011) and NEISS-CADES (2004-2013) data show pediatric ED visits associated with codeine-containing **analgesic** products
- NEISS-CADES data found pediatric ED visits related to **cough and cold** products
- Epidemiologic data on pediatric serious adverse events related to codeine-containing products are limited.
- There are no data on pediatric deaths that can distinguish codeine from other opioid products

Summary Points

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Summary Points on Utilization, and Epi Data Related to Safety, of Codeine-Containing Products in Pediatric Patients

- Over 2010-2014, although total OTC sales of codeine-containing products and prescription use by pediatric patients decreased, pediatric prescription use remains high.
- There are both FAERS and epidemiological data case reports of respiratory depression or respiratory problems in pediatric patients after use of codeine-containing products – both for cold/cough & analgesic uses.
- Two emergency department data sources showed pediatric ED visits for ADRs associated with codeine-containing analgesics.

Summary Points on Interpretation of the Utilization, and Epi Data on Safety, of Codeine-Containing Products in Pediatric Patients

- FAERS, NEISS-CADES, and DAWN largely cannot be used for reliable national estimates of codeine product related ADEs in the pediatric population.
- But still had respiratory depression/problem cases in both FAERS & NEISS-CADES.
- Cannot determine TRUE magnitude of problem, cannot get incidence rates.
- But also cannot conclude no problem, no risk.
- Taken all together, and given continuing high pediatric use of codeine-containing products, **these data do raise concern.**

Acknowledgements

- Gerald Dal Pan, MD
- Grace Chai, Pharm.D.
- Cindy Kortepeter, Pharm.D.
- Robert Levin, MD
- David Moeny, R.Ph., MPH
- Tracy Pham, Pharm.D.
- Eileen Wu, Pharm.D.

Joint Pulmonary-Allergy Drugs and Drug Safety and Risk Management Advisory Committee Meeting

FDA Charge to the Committee

Sally Seymour, MD
Deputy Director for Safety
Division of Pulmonary, Allergy, and Rheumatology Products
Center for Drug Evaluation and Research
Food and Drug Administration
December 10, 2015

Key Points

- Variability in codeine metabolism based upon CYP2D6 activity
- Reports of respiratory depression and death in pediatric patients
- In 2013, FDA contraindicated the use of codeine for postoperative pain management in children who have undergone tonsillectomy and/or adenoidectomy
- Some regulatory agencies have further restricted use of codeine for both cough and analgesia in pediatric patients

Question 1

DISCUSSION: Discuss the available data on the safety of codeine use for cough in pediatric patients. Please address the following age groups in your discussion:

a) children 0 to younger than 6 years of age;

b) children 6 to younger than 12 years of age;

c) children 12 to younger than 18 years of age.

Question 2

DISCUSSION: Discuss the available data on the safety of codeine use for pain in pediatric patients. Please address the following age groups in your discussion:

a) children 0 to younger than 6 years of age;

b) children 6 to younger than 12 years of age;

c) children 12 to younger than 18 years of age.

Question 3

VOTE: Based upon the discussion of the available safety data with codeine, should the current contraindication for codeine (for pain management in the post tonsillectomy and adenoidectomy setting) be expanded to a contraindication for codeine use for any pain management in children?

As per 21 CFR 201.57c(5), a drug should be contraindicated only in those clinical situations for which the risk from use clearly outweighs any possible therapeutic benefit. Only known hazards, and not theoretical possibilities, can be the basis for a contraindication.

a) Yes – contraindicate for any pain management in children younger than 6 years of age

b) Yes – contraindicate for any pain management in children younger than 12 years of age

c) Yes – contraindicate for any pain management in children younger than 18 years of age

d) No – no change to current contraindication

Provide the rationale for your recommendation and any other labeling recommendations you may have.

Question 4

VOTE: Based upon the discussion of the available safety data with codeine, should codeine be contraindicated for the treatment of cough in children?

As per 21 CFR 201.57c(5), a drug should be contraindicated only in those clinical situations for which the risk from use clearly outweighs any possible therapeutic benefit. Only known hazards, and not theoretical possibilities, can be the basis for a contraindication.

a) Yes – contraindicate for cough in children younger than 6 years of age
b) Yes – contraindicate for cough in children younger than 12 years of age
c) Yes – contraindicate for cough in children younger than 18 years of age
d) No – no change to current contraindication

Provide the rationale for your recommendation and any other labeling recommendations you may have.

Question 5

VOTE: Based upon the discussion of the available safety data with codeine, should codeine be removed from the FDA monograph for over the counter (21CFR341.1; 21CFR341.90) use for the treatment of cough in children?

a) Yes – remove codeine from the monograph for children younger than 6 years of age
b) Yes – remove codeine from the monograph for children younger than 12 years of age
c) Yes – remove codeine from the monograph for children younger than 18 years of age
d) No – no change to the current monograph for codeine.

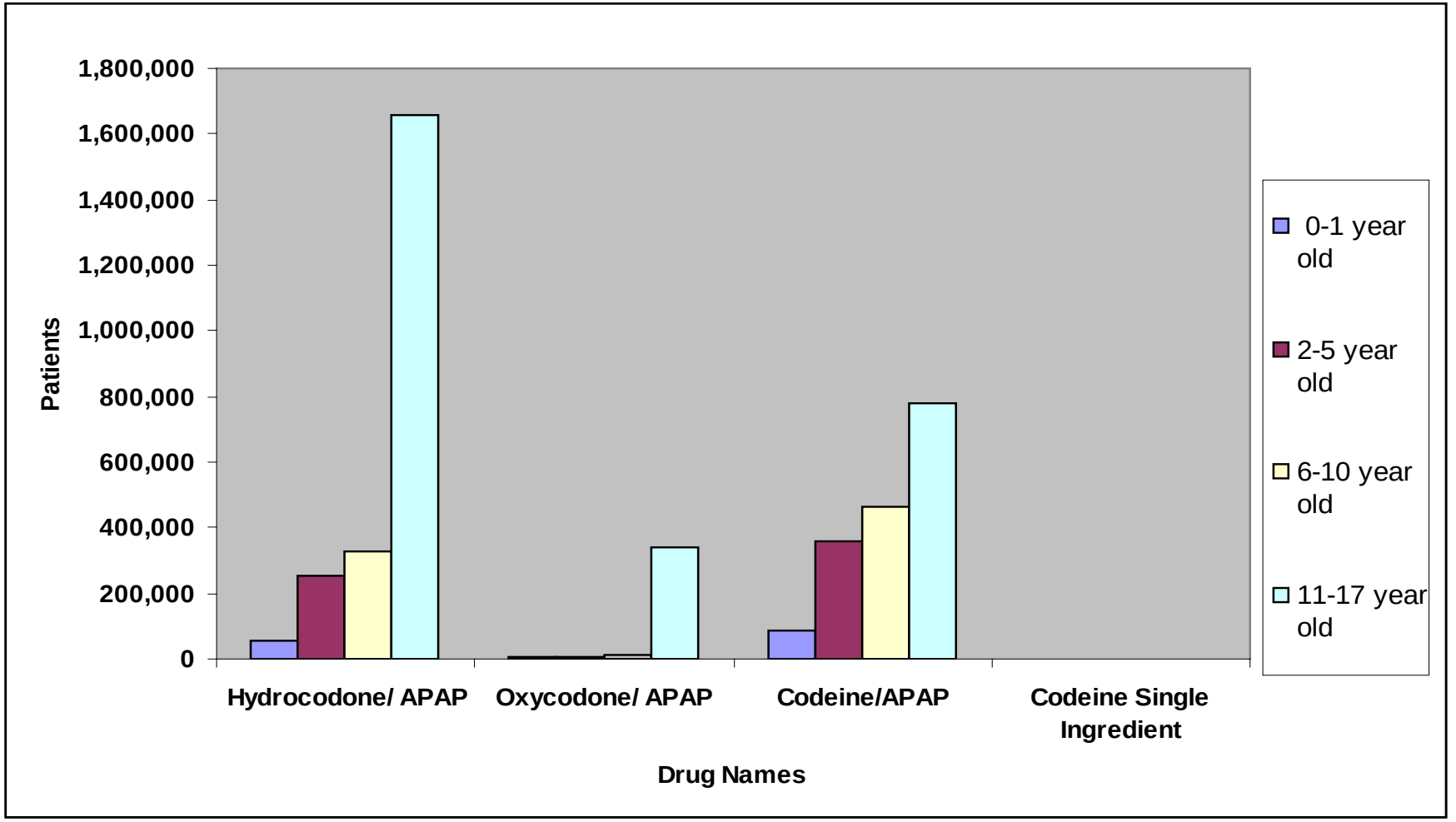
Provide the rationale for your recommendation and any other recommendations you may have.

Thank you

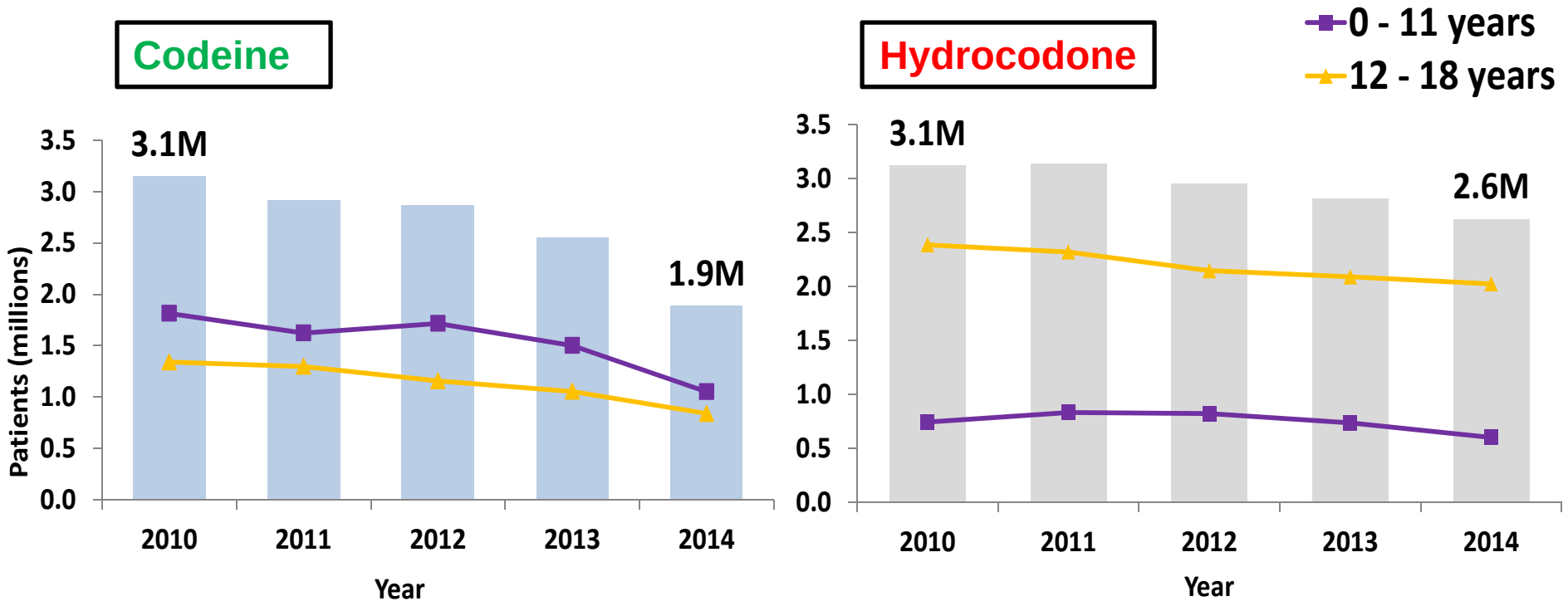
Backup Slides Shown

Nationally Estimated Number Of Pediatric Patients (0-1, 2-5, 6-10,11-17 year old) Receiving Dispensed Prescription for Selected Opioids from U.S. Outpatient Retail Pharmacies, Year 2011

Source: IMS, Total Patient Tracker, Extracted Sept, 2012



Total codeine: Pediatric use (0-18 years)



National estimates of total pediatric patients (0-18 years*) who received dispensed prescriptions for codeine or hydrocodone products from U.S. outpatient retail pharmacies

*Patient age groups are inclusive of all patients up to the day before their next birthday. For example, patients aged 0 - 16 years includes patients aged 16 years and 11 months.

Source: IMS Health, Vector One®: Total Patient Tracker. Years 2010 through 2014. Data extracted June 2015.

Database Description
OTC International Market Tracking

- Nationally tracks outpatient retail sales of OTC products
  - Represents 70% of OTC retail sales universe

- Sample of retail stores includes:
  - Drug stores: 19,900+ stores
  - Grocery stores with pharmacy: 14,500+ stores
  - Mass merchandisers (excluding Wal-Mart and Club stores): 3,200+ stores

NEISS-CADES 2004-2013: Codeine-containing ED Visits by Drug Product and Age Group

Product	Age Group (Years)				
	<2	2-5	6-11	12-18	Total
Cough and Cold Products					
Codeine/Promethazine	7	13	5	6	31
Codeine/Guaifenesin	5	6	3	11	25
Codeine/Guaifenesin/Pseudoephedrine	0	2	0	1	3
Unspecified codeine-containing cough and cold products	2	5	3	4	14
Total	14	26	11	22	73
Analgesic Products					
Acetaminophen/Codeine	26	54	43	111	234
Codeine	5	2	14	5	26
Aspirin/Butalbital/Caffeine/Codeine	1	0	0	0	1
Total	32	56	57	116	261

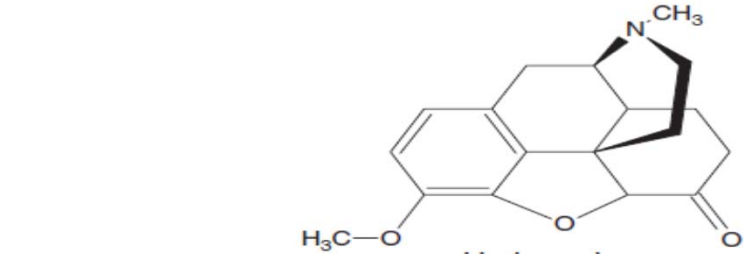
Recap of Epidemiological Emergency Dept. (ED) Visits Data Results

- DAWN national estimates **roughly 600-1700 pediatric ED visits/year** for codeine-containing analgesic products (2004-2011)
- NEISS-CADES ED visit case counts, for years 2004-2013 combined, from a 63 hospital sample (in patients<19 years old) were:

  -- 73 ED visits for codeine-containing cold/cough products, with 2 adverse drug events (ADE) with clinical manifestation of somnolence/dyspnea

  -- 261 ED visits for codeine-containing analgesic products, with 13 ADEs with manifestation of respiratory problems/somnolence

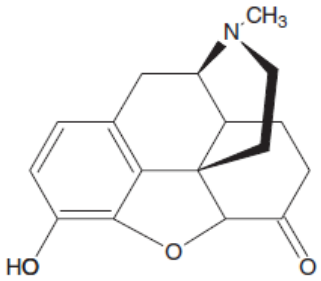
Hydrocodone Metabolism (Hydromorphone (<3% of the circulating parent hydrocodone)



Hydrocodone
(12x higher affinity for mu receptor than codeine)

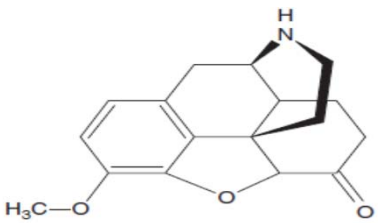
CYP2D6
(14%)

CYP3A4
(20%)



Hydromorphone

(10-30 x higher affinity for mu receptor than hydrocodone)

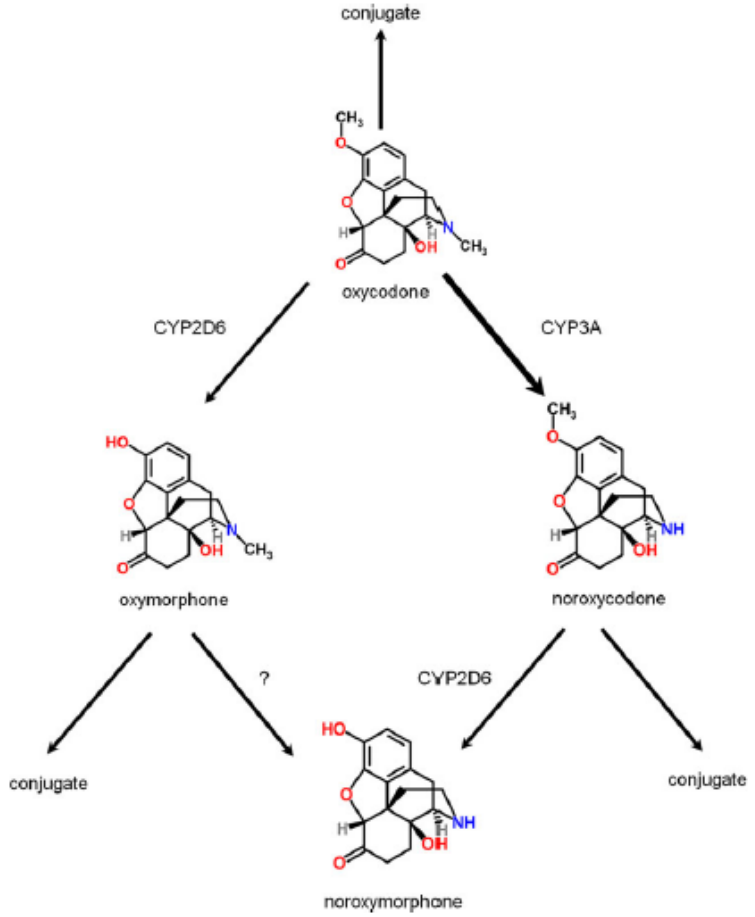


Norhydrocodone

(inactive)

Otton et al. *Clin Pharm Ther* 1993.

Oxycodone metabolism (Oxymorphone is present in the plasma only at low concentrations)



- Very low circulating concentrations of oxymorphone have been observed following a single oral dose of oxycodone; the AUC ratios oxymorphone to parent drug were 0.01